

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-519

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
Division Name: Psychiatry Products
HFD# 130
Review Completion Date: 12/14/07.

NDA number: 21-519.

Serial number/stamp-date/type of submission: N-000, AZ / June 21, 2007 / Response to Approvable Letter / Major amendment, multi-disciplinary; and N-000, BP / November 20, 2007 / final reports for nonclinical studies submitted as audited draft reports in the earlier submission.

Information to sponsor: Yes (X) No ()

Sponsor: Solvay Pharmaceuticals.

Drug:

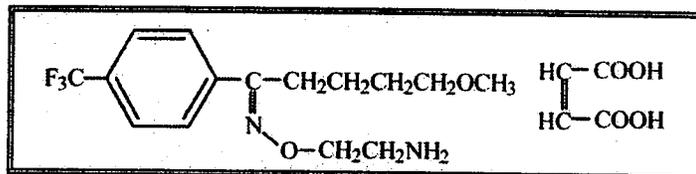
Generic Name: fluvoxamine maleate.

Trade Name: Luvox.

Molecular Formula / Molecular weight: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ / 434.41.

USAN Name: 5-methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate.

Structure:



Drug Class: Selective serotonin reuptake inhibitor (SSRI).

Indication: Obsessive-Compulsive Disorder (OCD) in adults and children and adolescents.

Clinical formulation: tablets; 25, 50, and 100 mg strengths.

Route of administration: oral.

Proposed clinical Use: For the treatment of Obsessive-Compulsive Disorder (OCD). According to the Sponsor's draft labeling, Luvox will be used in adult and pediatric populations: in adults, starting at 50 mg, with a maximum recommended daily dose of 300 mg; in children and adolescents, starting at 25 mg, with maximum recommended daily dose of 200 mg for children up to age 11 and 300 mg for adolescents.

Previous clinical experience: Luvox was approved for treatment of Obsessive-Compulsive Disorder under NDA 20-243 (12/5/94) and marketed by Solvay until 2002.

Several (12) generic formulations of Luvox were approved in the US in 2000-2002. Luvox is currently approved in several other countries.

Disclaimer: Where feasible, the Sponsor's figures and tables were incorporated directly into this review and noted as such.

Studies within this submission [the response to the Pharmacology/Toxicology issues was provided in volumes 1-3 of the paper submission]:

The Sponsor's summary response to the specific Pharmacology issues is provided in volume 1, pages 0002-0005.

Information on specifications for impurities in the drug substance, as provided in Attachment 2 (volume 1, pages 0027-0032), and in the drug substance, as provided in Attachment 7, volume 2, pages 0611-0620, were also considered for this review.

The 4 [audited draft] study reports that support their response have also been provided in the current submission (attachments 3-6, volumes 1-2). [Subsequently, in response to a request by the Agency, the Sponsor provided final reports for these studies (N-000, BP, letter-dated 11/19/2007, stamp-dated 11/20/2007); see Appendix to this review.]

Appears This Way
On Original

Table of Contents for this Review

1	PHARMACOLOGY/TOXICOLOGY (IMPURITY AND DEGRADANT) ISSUES ADDRESSED IN THIS SUBMISSION:	4
1.1	ACTION REQUESTED BY THE AGENCY IN OUR 11/16/06 AE LETTER:	4
1.2	THE SPONSOR'S RESPONSE:	5
1.3	THIS REVIEWER'S GENERAL COMMENTS/CONCLUSIONS:	5
1.4	COMMENTS ON THE INADEQUACY OF THE GENERAL TOXICITY STUDY TO QUALIFY FLUVOX KETONE: 7	7
2	OVERALL CONCLUSIONS:	8
3	RECOMMENDATIONS:	8
4	INFORMATION TO BE COMMUNICATED TO THE SPONSOR:	9
5	LABELING:	9
6	SIGNATURES	10
7	APPENDIX: REVIEW OF THE 4 TOXICITY STUDIES SUBMITTED TO QUALIFY THE IMPURITIES:	11
7.1	AMES TEST	12
7.2	MOUSE LYMPHOMA TK ASSAY	15
7.3	14-DAY GENERAL TOXICITY STUDY IN RATS (BASED ON FINAL REPORT)	17
7.4	EMBRYO-FETAL DEVELOPMENT STUDY IN RATS	19

**1 PHARMACOLOGY/TOXICOLOGY (IMPURITY AND DEGRADANT)
ISSUES ADDRESSED IN THIS SUBMISSION:**

1.1 Action requested by the Agency in our 11/16/06 AE letter:

For Luvox, with a maximum recommended human daily dose of 300 mg, the threshold for qualification of impurities in drug substance is 0.15% (ICH Q3A (revision 1) Guidance, 2003), which is higher than the earlier recommended 0.1% threshold (ICH Q3A Guidance, 1996), and the threshold for qualification of degradants in drug product is 0.2% (ICH Q3B Guidance, 1996).

In our 11/16/06 AE letter the following PT approvability issues were communicated:

Pharmacology/Toxicology Review

The specification for [redacted] in the drug product is set at [redacted] which is above the threshold for qualification (i.e., above 0.2%). Based on the most recent stability data, it appears that you are unable to lower this specification. Consequently, you will need to qualify this impurity/degradant in the following studies prior to approval:

- a general toxicology study in one species, of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and
- an embryofetal development study in one species.

The specification for [redacted] in the drug substance is set at [redacted] which is above the threshold for qualification (i.e., above 0.15%). You have indicated that you intend to lower this specification, but have not provided us with documentation of your revised specification. Such documentation or qualification of this impurity in the studies listed above will be needed prior to approval. If qualification is required, this impurity is currently considered to be qualified for embryofetal toxicity, but not for genotoxicity or general toxicity, as communicated in our previous AE letter (dated 2/9/04).

Although the [redacted] is considered to be adequately qualified for the current [redacted] specification in drug substance and product, the [redacted] level of this impurity in the Ames test will not be adequate to qualify specifications higher than [redacted].

In brief, the only Pharmacology/Toxicology concerns related to qualification of [redacted] : specified at [redacted] : specified at [redacted] (requiring the full complement of qualifying studies), and [redacted] (requiring an Ames test, if specified at [redacted]).

Additionally, the following PT Request for Post-Marketing Study Commitment for a juvenile animal study was communicated:

b(4)

b(4)

b(4)

b(4)

Request for Post-Marketing Study Commitment

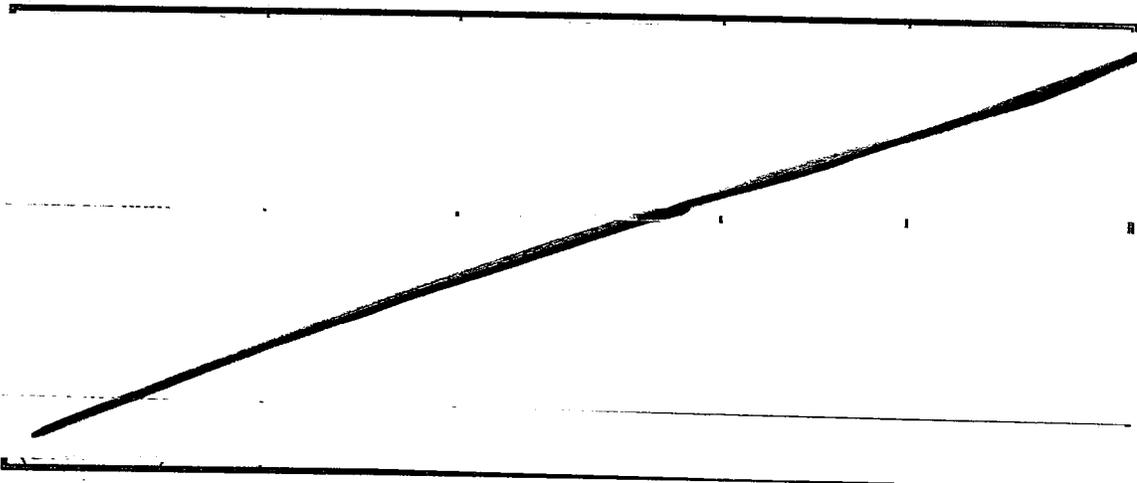
1. We note that Luvox has not yet been evaluated in juvenile animals. Although we previously requested (in our Approvable letter dated 2/9/04) that you conduct juvenile studies in rodent and non-rodent, our thinking on juvenile studies has evolved and we will only require a juvenile study in the rat. As previously communicated (in our Approvable letter dated 2/9/04), the impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in this study.

1.2 The Sponsor's response:

The Sponsor has provided their written response to the Pharmacology/Toxicology issues communicated in our 11/16/06 AE letter (pages 0002-0005, volume 1, this submission). In brief, they have tightened the specification for [redacted] from [redacted] and they feel that the [redacted] have been qualified in the four non-clinical studies that they have submitted (draft study reports in this submission; the final reports have been subsequently submitted studies under N-000, BP, letter-dated 11/19/2007, stamp-dated 11/20/2007), see table, below.

b(4)

Table 1. Summary of studies provided in the current submission [of the impurities/degradants tested, we had only asked for further qualification of [redacted]



b(4)

1.3 This Reviewer's general comments/conclusions:

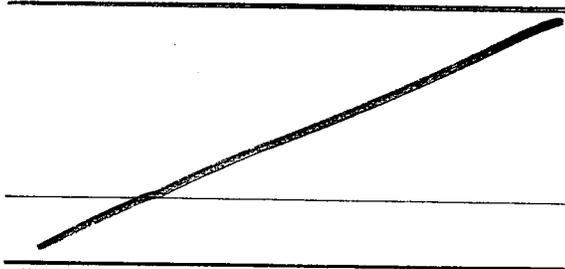
In our AE letter (dated 11/16/06), we only had concerns about inadequate qualification of [redacted] (regarding all 4 non-clinical studies), and [redacted] (regarding an Ames test, if specified at [redacted]).

b(4)

The Sponsor has lowered the specification for [REDACTED] (see volume 1, page 031 in Attachment 2 of this submission), a level that would not require qualification.

b(4)

Table 2. Specifications for drug substance and drug product (from Attachment 2 and Attachment 7, respectively) provided in this submission.



b(4)

*: controlled in substance, and reported in drug product, but not specified there.

[These appear to be the same specifications that were reviewed in the previous submission, except that the specification for [REDACTED] has been lowered from [REDACTED] none of the specifications has been increased.]

b(4)

The Sponsor has provided reports for the 4 studies [see reviews in Appendix] that we requested to qualify [REDACTED]: 1) a general toxicity study in one species (rat) of at least 14-days duration (comparing fluvoxamine alone and fluvoxamine spiked with [REDACTED]); 2) tests for in vitro genotoxicity, including a) an Ames test (with fluvoxamine spiked with [REDACTED]) and b) a mouse lymphoma tk assay (with fluvoxamine spiked with [REDACTED]); and 3) an embryo-fetal developmental study (comparing fluvoxamine alone and fluvoxamine spiked with [REDACTED]). None of these studies indicated any increased toxicity due to the presence of [REDACTED]. These studies would serve to qualify [REDACTED] content in the in vitro genotoxicity tests) and the Sponsor has retained the previous specification of [REDACTED] for this impurity in drug product. [See comments on the inadequacies of the general toxicity study in the next section of this review.]

b(4)

The Sponsor has retained the [REDACTED] specification for the [REDACTED] which we accepted as adequately qualified, although it had only been tested in the previous Ames tests to [REDACTED] in the current submission, they have provided an Ames test which would support qualification of this impurity [REDACTED]

b(4)

[In the current submission, the Sponsor has proposed to use drug substance from an alternative supplier, which uses a different synthesis scheme. The Chemistry Reviewer for this submission (Dr. David Claffey, Ph.D.) noted use of a new reagent in this synthesis, namely [REDACTED] which is an [REDACTED] and consequently suspected to be genotoxic. The issues regarding this reagent were resolved during this review cycle: the DMF holder has agreed to include a specification in the drug substance which would limit the dose of this impurity administered to humans to no more than [REDACTED] (see Dr. Claffey's review dated 12/10/07), which is considered to be an acceptable amount for an impurity known or suspected to be genotoxic.]

b(4)

1.4 Comments on the inadequacy of the general toxicity study to qualify [REDACTED]

b(4)

It should be noted that in our most recent AE letter (dated 11/16/2006), we stated that the general toxicity study for qualification of [REDACTED] should include microscopic examination of the standard battery of tissues; this requirement was made explicit in that letter because the Sponsor had submitted a 14-day general toxicity study without complete histopathological assessment for qualification of other impurities in response to our previous AE letter (dated 2/9/04). Although a full necropsy was conducted in the current study, (again) only selected tissues (adrenals, gross lesions, kidney, and liver) were examined microscopically. The Sponsor has provided no explanation for this deficiency.

b(4)

Additionally, it should be noted that under the current specification of [REDACTED] patients receiving the maximum recommended human dose of 300 mg could be exposed to up to [REDACTED] per day, a relatively small, but not insignificant amount. For these reasons, an adequate general toxicity study, including full histopathological assessment, should be required to support qualification of this impurity/degradant. If it is not possible for the Sponsor to obtain full microscopic analysis on the remaining fixed tissues from the current study, they should conduct another study, including full histopathological assessment.

b(4)

However, it is this Reviewer's opinion that this deficiency could be addressed post-marketing, rather than being required pre-approval, because: 1) there were no microscopic findings for adrenals, gross lesions, kidney, or liver (hepatocellular hypertrophy was present in males in both treated groups), and no changes in organ weights (adrenals, brain, heart, kidney, liver, mandibular, mesenteric, popliteal lymph nodes, ovaries, pituitary, prostate, spleen, testes + epididymides, thymus, thyroids + parathyroids) or in clinical chemistry or hematology parameters that would indicate changes attributable to either drug treatment (fluvoxamine alone or spiked with impurity); and 2) the results already obtained did not reveal any serious overt toxicity, such as death or ill health.

The current rat toxicity study could provide safety margins for [REDACTED] at the MRHD of 300 mg/day of fluvoxamine of 96-fold on a mg/kg basis (assumed to be relevant for gastrointestinal toxicity) and ~16-fold on a mg/m² basis (assumed to be relevant for systemic toxicity). [For the MRHD of 300 mg/day and the specification of [REDACTED] patients would be exposed to [REDACTED] per day; for a 60 kg adult this would be [REDACTED]. In the rat study, at 80 mg/kg fluvoxamine and [REDACTED] rats were exposed to [REDACTED]

b(4)

2 OVERALL CONCLUSIONS:

The only Pharmacology/Toxicology issues that prevented approval of this NDA in the previous review cycle, as communicated in our most recent AE letter (dated 11/16/06), concerned inadequate qualification of [REDACTED] at [REDACTED] (regarding all 4 non-clinical studies), and [REDACTED] (regarding an Ames test, if specified at [REDACTED]). In the current submission, the Sponsor has adequately addressed these issues: they have lowered the specification for [REDACTED] for an amount that does not require qualification; provided studies that will qualify [REDACTED] (but see caveat, below); and an Ames test that will support qualification of [REDACTED] (although the current specification of [REDACTED] was considered adequately qualified by previous studies).

b(4)

It should be noted that the repeated-dose general toxicity study that was needed to support qualification of [REDACTED] was not strictly adequate, because full histopathological assessment was not conducted, as explicitly requested in our most recent AE letter (dated 11/16/06). However, it is this Reviewer's opinion that this can be addressed in a post-marketing commitment (see discussion, above). [REDACTED]

b(4)

There are no Pharmacology/Toxicology issues that would prevent the Approval of this NDA.

3 RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, this NDA may be APPROVED.

However, the Sponsor will need to agree to post-market commitments for the following issues:

- [REDACTED] and
- to conduct a juvenile animal study in one species; impurities requiring qualification should also be tested in this study.

b(4)

Appears This Way
On Original

4 INFORMATION TO BE COMMUNICATED TO THE SPONSOR:

PHARMACOLOGY/TOXICOLOGY POST-MARKETING COMMITMENTS:

You did not conduct microscopic examination of the standard battery of tissues in the general toxicity study that you submitted to support qualification of _____, as we explicitly requested in our most recent Approvable letter (dated 11/16/2006). Consequently, you will need to address this issue by conducting complete microscopic assessment on tissues from that study or, _____

b(4)

As communicated to you in our Approvable letter dated 11/16/06, we note that Luvox has not yet been evaluated in juvenile animals. Although we previously requested (in our Approvable letter dated 2/9/04) that you conduct juvenile studies in rodent and non-rodent, our thinking on juvenile studies has evolved and we will only require a juvenile study in the rat. As previously communicated (in our Approvable letter dated 2/9/04), the impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in this study.

5 LABELING:

In our 11/16/06 AE letter, the following comments were communicated to the Sponsor:

- Under CLINICAL PHARMACOLOGY/ Pharmacodynamics, if you want to change labeling to include _____ you will need to resubmit the studies that support those claims.
- Under PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility/Carcinogenicity, the first sentence _____ should be deleted, based on the revised labeling for Impairment of Fertility and Pregnancy sections. We neglected to remove this sentence in the labeling communicated in the previous AE letter (2/9/04).
- Under PRECAUTIONS: Impairment of Fertility and Pregnancy/Teratogenic Effects sections, the route of dosing (oral) should be included. We neglected to include this in the labeling communicated in the previous AE letter (2/9/04).

b(4)

b(4)

In their labeling submitted in the current response to AE, the Sponsor addressed the last 2 comments by removing the sentence we asked to be removed and by adding the "oral" route

in the Impairment of Fertility section and in the first paragraph of the Pregnancy section; I assume their failure to similarly clarify the oral route in the second and third paragraphs of the Pregnancy section was an oversight. "We appreciate that you clarified the route of administration in the Impairment of Fertility section and in the first paragraph of the Pregnancy section; we have also clarified the route in the second and third paragraphs of the Pregnancy section."

They did not remove the [REDACTED] and (as far as I can tell) did not resubmit the studies that support those claims. We will again strike that wording, with the same request: "As communicated to you in our 11/16/07 Approvable letter, if you want to change labeling to include [REDACTED] you will need to resubmit the studies that support those claims." [On 11/30/07, these changes were made in our revisions to the Sponsor's proposed labeling; the comments explaining our changes were also provided.]

b(4)

6 SIGNATURES

Linda H. Fossom, Ph.D., Reviewing Pharmacologist *{see appended electronic signature page}*

Barry Rosloff, Ph.D., Supervisory Pharmacologist *{see appended electronic signature page}*

7 APPENDIX: REVIEW OF THE 4 TOXICITY STUDIES SUBMITTED TO QUALIFY THE IMPURITIES:

The following 4 study reports were originally submitted as audited draft reports in the submission currently under review. Subsequently, in response to a request by the Agency, the Sponsor provided final study reports (N-000, BP, letter-dated 11/19/2007, stamp-dated 11/20/2007; see table of contents, below). The final study reports are reviewed here. [According to the cover letter which accompanied the final reports, "The finalization of these audited draft reports did not result in any scientific changes to the results or conclusions. Quality assurance statements were completed and the reports were signed accordingly." They provided "a listing of the administrative changes to each study report that were made since the submission of the audited draft reports" (provided in Attachment 1 of the cover letter).]

Table 3. Table of Contents for submission of final reports for non-clinical studies (NDA 21-519, N-000, BP, letter-dated 11/19/2007, stamp-dated 11/20/2007).

TABLE OF CONTENTS		<u>Volume</u>	<u>Page</u>
ATTACHMENT 1		1	0002
Fluvoxamine Final Report Changes.....		1	0003
FLUVOXAMINE MALEATE SPIKED WITH _____ REVERSE MUTATION IN FIVE HISTIDINE- REQUIRING STRAINS OF SALMONELLA TYPHIMURIUM (S114.7.003)		1	0007
FLUVOXAMINE MALEATE SPIKED WITH _____ MUTATION AT THE THYMIDINE KINASE (TK) LOCUS OF MOUSE LYMPHOMA L5178Y CELLS (MLA) USING THE MICROTITRER FLUCTUATION TECHNIQUE (S114.7.004)		1	0082
FLUVOXAMINE MALEATE: 14 DAY ORAL (GAVAGE) ADMINISTRATION COMPARATIVE TOXICITY STUDY IN THE RAT WITH FLUVOXAMINE MALEATE AND FLUVOXAMINE MALEATE SPIKED WITH _____ _____ (S114.7.005)		1	0142
FLUVOXAMINE MALEATE SPIKED WITH _____ _____ AND _____ : ORAL (GAVAGE) STUDY OF EMBRYO-FOETAL DEVELOPMENT IN THE RAT (S114.7.006)		2	0395

b(4)

b(4)

b(4)

b(4)

7.1 AMES TEST

Fluvoxamine maleate spiked with [REDACTED] Reverse mutation in five histidine-requiring strains of Salmonella typhimurium. [Solvay report no. S114.7.003; conducted by [REDACTED] (study no. 65/311), final report (submission stamp-dated 11/20/07: volume 1, pages 0007-0081), GLP/QA, experimental work started 2/20/07, completed 4/12/07, signed by study director 8/13/07].

b(4)

Key study findings:

- Valid and negative: fluvoxamine spiked with [REDACTED] was negative in the Ames test, with and without metabolic activation.

b(4)

Methods: Fluvoxamine maleate (batch no. 0136) spiked with [REDACTED] (batch no. 0122) and [REDACTED] [batch no. ARS9927AA, [REDACTED]), formulated in DMSO, was tested for mutagenicity in 5 Salmonella typhimurium tester strains: TA98, TA100, TA1535, TA1537, TA102; at concentrations up to 2000 ug/plate (97% fluvoxamine maleate [REDACTED] total impurities), ± S9 (range-finding study with spiked drug in TA100, ± S9, indicated that ≥1000 ug/plate resulted in complete killing or marked reduction in revertants). Two experiments were conducted: 1) standard plate incorporation assay at doses 0.64-2000 ug/plate, 5-fold apart, ± S9; and 2) standard plate incorporation assay at doses 3.3-2000 ug/plate, 2.5-fold apart, ± S9, with 30-min pre-incubation for the +S9 condition; for both studies, triplicate plates were assessed for all drug conditions and 5 plates were assessed for negative controls. Test drug solutions were assayed for each of the 3 components and found to be within 10% of nominal concentrations (in at least 2/3 assays).

b(4)

Results: Valid and negative: No indication of mutagenicity at any conditions, up to cytotoxic doses (i.e., no revertant colonies or thinning of bacterial background lawn ± decrease in revertants), ± S9, in replicate assays (standard assay, plus the replicate assay, with pre-incubation for +S9 and more narrowly-spaced doses); positive controls gave robust responses; values for negative controls were within the 99% reference ranges for historical controls provided by the facility (based on ~500 plates for each strain ± S9). Only the results of the second assay are provided below, since both tests were clearly negative and used the same positive controls, and the second assay provided a better test (more closely spaced drug concentrations, preincubation with S9).

Appears This Way
On Original

Table 4. Fluvoxamine maleate spiked with [REDACTED] did not increase revertants in an Ames test in the absence of metabolic activation. [Sponsor's table excerpted directly from pages 30-31 out of 75 of the final study report, pages 0036-0037, volume 1, submission stamp-dated 11/20/07.]

b(4)

Table 3: Fluvoxamine Maleate spiked with [REDACTED] summary of mean revertant colonies (-S-9) - Experiment 2

Substance	Dose Level µg/plate	TA98	TA100	TA1535	TA1537	TA102
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
DMSO	100 µl	17 ± 3	99 ± 10	19 ± 8	16 ± 4	326 ± 42
Fluvoxamine Maleate spiked [REDACTED] [REDACTED] [REDACTED]	3.277	NT	NT	NT	NT	346 ± 34
	8.192	NT	NT	NT	NT	330 ± 7
	20.48	23 ± 3	103 ± 9	22 ± 7	13 ± 4	356 ± 38
	51.2	20 ± 5	107 ± 9	19 ± 7	13 ± 3	310 ± 34
	128	22 ± 10	120 ± 10	17 ± 4	9 ± 4	278 ± 15
	320	27 ± 7	95 ± 4	11 ± 3	10 ± 3	227 ± 39
	800	22 ± 3	77 ± 10	12 ± 6	13 ± 3	37 ± 10 (S)
	2000	5 ± 4 (S)	11 ± 2 (S)	8 ± 5 (S)	5 ± 2	NT
Positive controls	Compound	2NF	NaN ₃	NaN ₃	AAC	MMC
	Dose Level	5 µg	2 µg	2 µg	50 µg	0.2 µg
	Mean ± SD	937 ± 90	1040 ± 40	721 ± 49	156 ± 103	679 ± 27
SD	Standard deviation					
NT	Not treated					
MMC	Mitomycin C					
2NF	2-Nitrofluorene					
NaN ₃	Sodium azide					
AAC	9-Aminoacridine					
S	: Slight thinning of background bacterial lawn					

b(4)

Table 5. Fluvoxamine maleate spiked with _____ did not increase revertants in an Ames test in the presence of (preincubation) metabolic activation. [Sponsor's table excerpted directly from pages 32-33 out of 75 of the final study report, pages 0038-0039, volume 1, submission stamp-dated 11/20/07.]

b(4)

Table 4: Fluvoxamine Maleate spiked with _____ summary of mean revertant colonies (+S-9) - Experiment 2

Substance	Dose Level µg/plate	TA98	TA100	TA1535	TA1537	TA182
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
DMSO	50 µl	32 ± 6	126 ± 7	17 ± 4	19 ± 7	270 ± 16
Fluvoxamine Maleate spiked _____ _____ _____	3.277	NT	NT	NT	NT	204 ± 17
	8.192	36 ± 7	97 ± 19	12 ± 4	15 ± 6	185 ± 22
	20.48	39 ± 7	106 ± 8	14 ± 4	19 ± 1	208 ± 28
	51.2	35 ± 8	94 ± 19	17 ± 9	23 ± 7	209 ± 12
	128	34 ± 3	86 ± 8	13 ± 6	22 ± 8	176 ± 15
	320	29 ± 7 (S)	73 ± 2 (S)	9 ± 5 (S)	18 ± 2 (S)	- (T)
	800	10 ± 2 (V+M)	43 ± 12 (V+M)	6 ± 1 (V+M)	- (T)	- (T)
	2000	- (T)	- (T)	- (T)	- (T)	NT
Positive controls	Compound	B[a]P	AAN	AAN	AAN	AAN
	Dose Level	10 µg	5 µg	5 µg	5 µg	20 µg
	Mean ± SD	379 ± 7	1722 ± 131	236 ± 45	129 ± 32	996 ± 272
SD	Standard deviation					
NT	Not treated					
AAN	2-Aminoanthracene					
B[a]P	Benzo[a]pyrene					
S	: Slight thinning of background bacterial lawn					
T	: Toxic, no revertant colonies					
V	: Very thin background lawn					
M	: Plate counted manually					

b(4)

7.2 MOUSE LYMPHOMA tk ASSAY

Fluvoxamine maleate spiked with [REDACTED] Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the [REDACTED] fluctuation technique. [Solvay report no. S114.7.004; conducted by [REDACTED] (study no. 65/311), final report (submission stamp-dated 11/20/07: volume 1, pages 0082-0141), GLP/QA, experimental work started 2/13/07, completed 4/3/07, signed by study director 8/13/07].

b(4)

Key study findings:

- Valid and negative: fluvoxamine spiked with [REDACTED] was negative for in vitro clastogenicity in the mouse lymphoma assay, with and without metabolic activation.

b(4)

Methods: Fluvoxamine maleate (batch no. 0136) spiked with [REDACTED] (batch no. 0122), formulated in DMSO, was tested for in vitro clastogenicity in L5178Y cells; in a cytotoxicity range-finding study up to a maximum concentration of 2230 ug/ml (precipitate formed at this concentration after 24 hr incubation); 50 ug/ml for 3 hr decreased RTG to 14% (-S9) and 26% (+S9) of control, but 25 ug/ml only decreased RTG to 86% (-S9) and 97% (+S9) of control; 25 ug/ml for 24 hr decreased RTG to 3% (-S9) of control, but 12.5 ug/ml only decreased RTG to 96% (-S9). For mutagenicity studies, cells were incubated with drug (or positive control or DMSO; duplicate flasks for each treatment, except only single flasks for positive controls) for 3 hr ±S9 or 24 hr -S9; after (washing and subculturing) 2-day expression period (with subculturing as necessary), cells were plated in 96-well plates for viability assessment (8 cells/ml x 0.2 ml/well for 7-8 days) or mutagenicity assessment (10⁴ cells/ml plus TFT at 3 ug/ml final concentration x 0.2 ml/well, 4 plates per treatment flask, for 11-12 days); apparently all counting of colonies was done manually.

b(4)

Test drug solutions were assayed for both components and found to be within 10% of nominal concentrations.

Results: Valid and negative: In experiment 1, treatment with fluvoxamine maleate spiked with [REDACTED] did not increase mutation frequency (MF) after 3-hr treatment in the absence of S9 (at concentrations up to 50 ug/ml, where RTG was decreased to 19% of control) or in the presence of S9 (at concentrations up to 60 ug/ml, where RTG was decreased to 21% of control), as shown in Table 3, below. In experiment 2, treatment with fluvoxamine maleate spiked with [REDACTED] did not increase mutation frequency (MF) after 24-hr treatment in the absence of S9 (at concentrations up to 20 ug/ml, where RTG was decreased to 8% of control); as seen in experiment 1, 3-hr treatment without S9 again did not increase MF in the absence of S9, as shown in Table 3, below. Negative controls were appropriate and positive controls gave robust responses in both experiments. The mutation frequencies represent large and small colonies, combined; however, analysis of positive controls showed that adequate induced mutation frequency was achieved for small colonies in the presence of S9 (>40% and >150 per million viable cells) and near-adequate induced mutation frequency was achieved for

b(4)

small colonies in the absence of S9 ($\geq 33\%$ and ≥ 131 per million viable cells, for both 3- and 24-hr treatments).

Table 6. Lack of mutagenicity of fluvoxamine maleate spiked with _____ in microwell mouse lymphoma gene mutation assays, conducted for 3 hr \pm S9 (Experiment 1, upper panel) and for 24 hr -S9 and 3 hr +S9 (Experiment 2, lower panel) [Sponsor's tables, excerpted directly from pages 32-33 out of 60 pages of the study report (volume 1, pages 0113-0114, submission stamp-dated 11/20/07).]

b(4)

**Table 7: Summary of results: Experiment 1
3 hour treatments in the absence and presence of S-9**

Treatment ($\mu\text{g/mL}$)	-S-9		Treatment ($\mu\text{g/mL}$)	+S-9	
	% RTG	MF§		% RTG	MF§
0	100	77.77	0	100	78.34
10	75	79.11	30	102	81.84
20	69	67.42	35	84	64.44
30	55	72.99	40	68	80.10
35	47	69.26	45	68	59.59
40	27	67.12	50	39	78.34
45	22	75.60	55	27	75.99
50	19	57.97	60	21	63.78
Linear trend		NS	Linear trend		NS
NQO			BP		
0.15	41	628.21	2	47	771.98
0.2	38	650.50	3	39	761.01

§ 5-TFT resistant mutants/ 10^6 viable cells 2 days after treatment
NS Not significant

**Table 8: Summary of results: Experiment 2
24 hour treatment in the absence of S-9, 3 hour treatment in the presence of S-9**

Treatment ($\mu\text{g/mL}$)	-S-9		Treatment ($\mu\text{g/mL}$)	+S-9	
	%RTG	MF§		%RTG	MF§
0	100	70.85	0	100	59.93
5	93	51.06	10	122	53.68
7.5	94	57.90	40	78	54.67
10	77	49.52	50	55	59.82
12.5	69	64.47	55	44	69.34
15	48	44.74	60	37	44.91
17.5	33	46.94	65	36	52.27
20	8	72.25	70	46!	49.87!
			75	16	61.88
Linear trend		NS	Linear trend		NS
NQO			BP		
0.05	74	450.58	2	52	516.84
0.1	34	719.25	3	43	679.27

§ 5-TFT resistant mutants/ 10^6 viable cells 2 days after treatment
%RTG Percent relative total growth (adjusted by day 0 factor for 24 hour treatment)
! Based on one replicate only
NS Not significant

7.3 14-DAY GENERAL TOXICITY STUDY IN RATS (based on final report)

Fluvoxamine maleate: 14 Day oral (gavage) administration comparative toxicity study in the rat with fluvoxamine maleate and fluvoxamine maleate spiked with _____
_____ [Solvay report no. S114.7.005; conducted by _____]

b(4)

(study no. 0065/314), final report (submission stamp-dated 11/20/07: volume 1, pages 0142-0245 and volume 2, pages 0246-0394), GLP (UK and OECD)/QA, first treatment on 2/8/07, pathology completed 7/30/07; signed by study director 8/20/07].

Key study findings:

- 80 mg/kg fluvoxamine (by oral gavage daily for 14 days), alone (unspiked) or spiked with _____ impurities: _____ plus vehicle control.
- No findings that would indicate increased toxicity due to the spiked impurities.
- Limitations: 1) histopathology assessment was only conducted on adrenals, gross lesions, kidney, and liver; 2) _____ nominal in the solution used on day 14 (but at nominal concentration on day 1, the only other solution that was analyzed; fluvoxamine concentration was appropriate when analyzed in solutions from both days); it should be noted that we do not require that all drug solutions be analyzed for drug content; although this unresolved discrepancy is worrisome, it would be more of a concern if the concentration determined by analysis had been less than the nominal concentration.

b(4)

b(4)

Methods: Male and female _____ :WI (Han) rats _____ 10/sex/group, 7-8 weeks old at start of dosing) were treated by oral gavage (10 ml/kg) with vehicle (0.5% poloxamer 188 + 1% methylcellulose in purified water), 80 mg/kg fluvoxamine maleate (batch no. 1024349-0008), or (presumably) 80 mg/kg fluvoxamine maleate spiked with _____ (batch no. MP0122) and _____ (batch no. ARS0428AA) [The Sponsor considered the 80 mg/kg dose to be the LOAEL in the previous 3-month toxicity study (report no H.114.499), based on "slight effects on the liver and vacuolation of hepatocytes."]; housed 5 same-sex/cage (it appears that all rats in a cage received the same treatment, since "Treatment group position in the cage battery were assigned using a set of random number permutations"), with food and water ad lib, on aspen wood chips bedding.

b(4)

Assessments: mortality, clinical signs, body weights, food consumption, ophthalmoscopy (pre- and in week 2), clinical pathology and hematology (at necropsy), urinalysis (in week 2); **full necropsy** on all rats; organ weights (adrenals, brain, heart, kidney, liver, mandibular, mesenteric, popliteal lymph nodes, ovaries, pituitary, prostate, spleen, testes + epididymides, thymus, thyroids + parathyroids); **limited histopathology** on all rats (only conducted on adrenals, gross lesions, kidney, and liver), toxicokinetics (on days 1 and 14, 2/sex/treatment at 0.5, 1, 3, 7, and 24 hr after dosing).

Drug solutions were prepared daily; solutions from days 1 and 14 were assayed for homogeneity and content of fluvoxamine and impurities [no drug was detected in vehicle samples; drug solutions appeared to be homogeneous (based on samples from top and bottom); amounts of drug and impurities agreed with nominal concentrations, except for _____ on day 14, which was ~3.5-fold nominal; the Sponsor could find no explanation for this (re-assay confirmed the amount, but the correct amount of _____ appeared to have been added), but concluded that "The impact of this single elevated dose of _____ was that the cumulative amount of: _____ received over 14 days was ca. _____ higher than the target amount."]

b(4)

Results: There were no unscheduled deaths. Clinical findings were limited to post-dosing salivation and/or mouth rubbing from day 8 (unspiked groups) or 6 (spiked groups), which resolved by 1 hr after dosing. There were no significant effects on body weights or food consumption; and no ophthalmoscopic findings. Clinical chemistry and hematology finding were limited to minor (<10%) changes in prothrombin time, fibrinogen, mean cell hemoglobin; decreased (13%) cholesterol in unspiked fluvoxamine males; with no effects on urinalysis. Effects on organs were limited to decreased (13%) spleen weights and increased (18%) ovary weights [but microscopic examination was not conducted on these organs] in unspiked fluvoxamine females; necropsy findings of large livers in treated (spiked and unspiked) males; histopathology findings in liver: increased incidence of (minimal) centrilobular hypertrophy in dosed males (3/10 unspiked, 4/10 spiked). Toxicokinetic analysis of fluvoxamine indicated that dosed rats were exposed to drug: no drug (<20 ng/ml) was found in control rats at any time point (on either day 1 or 14); fluvoxamine levels were detected in all dosed rats sampled at 0.5-7 hr, but undetectable at 24 hr; similar exposures were seen in spiked and unspiked groups, with higher exposures in females than males on day 1, but similar exposures in both sexes on day 14.

There were no findings in this study that would indicate increased toxicity due to the spiked impurities. It should be noted that full histopathology was not conducted (only adrenals, gross lesions, kidney, and liver were examined microscopically). Although it might be possible for the Sponsor to have full microscopic analysis conducted on the remaining fixed tissues (if they are still available), it seems unlikely that that analysis would be productive, because: 1) there were no microscopic findings for adrenals, gross lesions, kidney, or liver, and no changes in organ weights (adrenals, brain, heart, kidney, liver, mandibular, mesenteric, popliteal lymph nodes, ovaries, pituitary, prostate, spleen, testes + epididymides, thymus, thyroids + parathyroids) that would indicate changes attributable to either drug treatment; and 2) the short 14-day duration of drug treatment at a relatively (LOAEL) dose of fluvoxamine would be unlikely to produce changes detectable at histopathology.

Appears This Way
On Original

7.4 EMBRYO-FETAL DEVELOPMENT STUDY IN RATS

Fluvoxamine maleate spiked with _____
_____: Oral (gavage) comparative study of embryo-foetal
development in the rat. [Solvay report no. S114.7.006; conducted by _____
_____ (study no.
0065/313), final report (submission stamp-dated 11/20/07: volume 2, pages 0395-058),
GLP (UK and OECD)/QA, first treatment on 2/5/07, necropsy completed 2/21/07; signed
by study director 8/8/07].

b(4)

[The current Sponsor has previously submitted a Segment II embryo-fetal development study in rats, using higher doses (60, 120, and 240 mg/kg) than were used in the original study (where the high dose was 80 mg/kg), as a Phase 4 commitment (reviewed under an earlier submission to this NDA: N-000, 4T / June 23, 2003; review by this Reviewer finalized 2/9/2004). Comparisons to this study are made, below, where appropriate.]

Key study findings:

- 80 mg/kg fluvoxamine, alone (unspiked) or spiked with _____impurities: _____
_____ [dose of fluvoxamine considered approximately a LOAEL, based on previous studies]
- Administered by oral gavage to pregnant rats, GD 6-17, with necropsy/assessment on GD 20.
- No maternal toxicity.
- No significant embryo-fetal toxicity; specifically no increased toxicity attributable to spiked impurities.

b(4)

Methods: time-mated female _____:CD (SD) rats (_____
24/group, 8-10 weeks old at time of mating; delivered to _____ by gestational day 2 or
3) were treated by oral gavage (10 ml/kg) on gestational days 6-17 with vehicle (0.5%
poloxamer 188 + 1% methylcellulose in purified water), 80 mg/kg fluvoxamine maleate
(batch no. 1024349-0008), or (presumably) 80 mg/kg fluvoxamine maleate spiked with
_____ (batch no. ARS0428AA), _____
_____ [batch no. ARS9927AA/WRS02781 _____
_____ (batch no. MP0122), _____ (batch no. WSS014901), and
_____ (batch no. WRS027601) [The Sponsor considered the
80 mg/kg dose to be the highest NOAEL in a previously performed teratology study
(cited as Solvay report no. PDR 151/73872; where, the Sponsor says, no effects were
seen at the high dose of 80 mg/kg) and a developmental toxicity study (cited as report no
TX.114.07.05P CRO; where, the Sponsor says, a decrease in food consumption was seen
at 60 mg/kg)]; drug doses were prepared daily; housed individually, with food and water
ad libitum; measurements: mortality (twice daily), clinical signs, body weights and food
monitoring (GD 4, 6, 7, 8, 9, 12, 15, 17, 18, 20); necropsy on GD 20, with gross maternal
pathology and fetal pathology.

b(4)

Results: There were no significant effects on maternal variables (see table, below): no maternal mortality; no effect on maternal body weights or food consumption; slightly increased placental weight in treated groups (with statistical significance only in the unspiked group); no effects on numbers of implantation sites or corpora lutea; a slight (non-significant) increase in post-implantation loss in both unspiked and spiked groups. [NB Based on my review of the previous Segment II study (TX.114.07.05P CRO; see review by this Reviewer dated 2/6/04), maternal toxicity (decreased terminal weights, \pm gravid uterus weights and a single death) was seen at 240 mg/kg, but not at \leq 120 mg/kg; the developmental NOAEL was 60 mg/kg, based on increased resorptions and increased incidence of eye abnormality (folded retina) at \geq 120 mg/kg; and decreased fetal weights, decreased live litter size, and decreased number of ossified metatarsals at 240 mg/kg.]

Table 7. Maternal variables for Segment II study in rats comparing vehicle control with 80 mg/kg fluvoxamine alone (unspiked) or spiked with \ominus impurities: —

b(4)

[Data compiled from Sponsor's data.]

Parameter	Treatment		
	control	unspiked	spiked
Total pregnancy rate	23/24	24/24	24/24
Mortalities	0	0	0
Pregnant Females at termination	23	24	24
Mean implantation sites	12.7	12.7	12.8
Mean corpora lutea	15.1	14.3	15.4
Pre-implantation loss, %, per dam	13.2	10.1	15.5
Mean live fetuses	12.3	12.0	12.0
Mean dead fetuses	0.0	0.0	0.0
Mean early resorptions	0.4	0.7	0.8
Mean late resorptions	0.0	0.0	0.0
Post-implantation loss, %, per litter	3.2	5.1	6.1
Placental weight, g, per dam	0.57	0.62*	0.61

Embryo-fetal variables (see table, below): There were no effects on the number of live fetuses per litter or on fetal weights (males tended to weigh slightly (~5%) more than females in all groups). The apparent increase in external/visceral variations in both fluvoxamine groups were attributable to increased incidence of slight kidney cavitation in those groups (seen in only 1 fetus in control litters, but in 18 fetuses from 10 litters in the unspiked group and in 18 fetuses from 14 litters in the spiked group). [It should be noted that a tendency towards increased incidence of slight to moderate dilatation of the kidney pelvis was seen in the previous Segment II study with (unspiked) fluvoxamine, which was apparent at 240 mg/kg, but not (clearly) at 60 and 120 mg/kg.] There was no change in the incidence of skeletal variations with either fluvoxamine treatment.

Malformations were rare in all treatment groups: skeletal malformations were limited to 2 fetuses (in separate litters) from the unspiked fluvoxamine group; external/visceral malformations occurred slightly more frequently in the unspiked fluvoxamine group,

largely due to 3 fetuses (from 3 litters) with severely increased kidney cavitation in that group, compared to only 1 fetus from each of the other groups.

Table 8. Embryo-fetal variables for Segment II study in rats comparing vehicle control with 80 mg/kg fluvoxamine alone (unspiked) or spiked with— impurities:

b(4)

[Data compiled from Sponsor's data.]

Parameter	control	unspiked	spiked
Mean live fetuses/litter	12.3	12.0	12.0
Mean % males	47.1%	49.9%	52.6%
Mean fetus weights, g	3.84	3.82	3.79
Total litters examined	23	24	24
Total fetuses examined for external/visceral abnormalities	283	288	288
Total fetuses examined for skeletal abnormalities	142	145	144
Total fetuses with external/visceral variations (litters)	43 (20)	89 (22)	74 (21)
Total fetuses with skeletal variations (litters)	132 (23)	126 (23)	116 (24)
Total fetuses with external/visceral malformations (litters)	3 (3)	5 (4)	2 (2)
Total fetuses with skeletal malformations (litters)	0 (0)	2 (2)	0 (0)
Total fetuses with any malformations (litters)	3 (3)	5 (4)	2 (2)

Appears This Way
On Original

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Fossom
12/14/2007 12:25:13 PM
PHARMACOLOGIST

Barry Rosloff
12/14/2007 05:45:22 PM
PHARMACOLOGIST

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
Division Name: Psychiatry Products
HFD# 130
Review Completion Date: 11/12/06.

NDA number: 21-519.

Serial number/stamp-date/type of submission: N-000, AZ / May 17, 2006 / Response to
Approvable Letter / Major amendment, multi-disciplinary.

Information to sponsor: Yes (X) No ()

Sponsor: Solvay Pharmaceuticals.

Manufacturer for drug substance: same.

Drug:

Code Name: not provided.

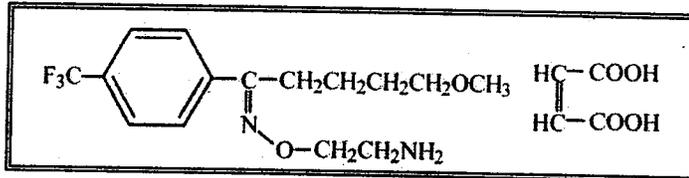
Generic Name: fluvoxamine maleate.

Trade Name: Luvox.

Molecular Formula / Molecular weight: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ / 434.41.

USAN Name: 5-methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate.

Structure:



Relevant INDs/NDAs/DMFs:

- [REDACTED] b(4)
- [REDACTED] b(4)
- [REDACTED] b(4)
- [REDACTED] b(4)
- NDA 20-243 (IR tablets, approved for OCD (12/5/1994), supported by P/T data submitted to NDA [REDACTED]; subsequently withdrawn by Commissioner (9/3/2003); sponsored by Solvay; b(4)
- NDA 22-033 (CR formulation): currently pending review, for treatment of Generalized Social Anxiety Disorder and Obsessive Compulsive Disorder; sponsored by Solvay;
- DMF [REDACTED]: describing manufacture of drug substance; held by Solvay Pharmaceuticals, Inc. b(4)

Drug Class: Selective serotonin reuptake inhibitor (SSRI).

Indication: Obsessive-Compulsive Disorder (OCD) in adults and children (aged) and adolescents.

Clinical formulation: tablets; 25, 50, and 100 mg strengths.

Route of administration: oral.

Proposed clinical Use: For the treatment of Obsessive-Compulsive Disorder (OCD). According to the Sponsor's draft labeling, Luvox will be used in adult and pediatric populations: in adults, starting at 50 mg, with a maximum recommended daily dose of 300 mg; in children and adolescents, starting at 25 mg, with maximum recommended daily dose of 200 mg for children up to age 11 and 300 mg for adolescents.

Previous clinical experience: Luvox was approved for treatment of Obsessive-Compulsive Disorder under NDA 20-243 (12/5/94) and marketed by Solvay until 2002. Several (12) generic formulations of Luvox were approved in the US in 2000-2002. Luvox is currently approved in several other countries.

Disclaimer: Where feasible, the Sponsor's figures and tables were incorporated directly into this review and noted as such.

Appears This Way
On Original

Appears This Way
On Original

Studies within this submission:

Attachment 12: a 3-page "Response to Pharmacology/Toxicology," which was supported by the following 4 study reports (Attachment 13), which had been previously submitted under their [REDACTED] and were reviewed in detail there.

- Report H0114.4.005X: Fluvoxamine maleate spiked with [REDACTED] Reverse mutation in five histidine-requiring strains of *Salmonella typhimurium*; b(4)
- Report H0114.4.006X: Fluvoxamine maleate spiked with [REDACTED] Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the [REDACTED] fluctuation technique; b(4)
- Report H0114.4.007X: Fluvoxamine maleate: 14 Day oral (gavage) administration comparative toxicity study in the rat with fluvoxamine maleate and fluvoxamine maleate spiked with [REDACTED] b(4)
- Report H0114.4.008X: Fluvoxamine maleate spiked with [REDACTED] Oral (gavage) comparative study of embryo-foetal development in the rat. b(4)

Appears This Way
On Original

Appears This Way
On Original

1 INTRODUCTION AND DRUG HISTORY:

1.1 Early background

Luvox (sponsored by Solvay) was approved for treatment of Obsessive-Compulsive Disorder (OCD) under NDA 20-243 on 12/5/94. That NDA was put under Application Integrity Policy (AIP) for chemistry irregularities. In an agreement with the Agency, Solvay withdrew NDA 20-243 (on 5/13/02) and submitted a new NDA for Luvox (the current NDA 21-519) on 7/1/02.

No non-clinical pharmacology or toxicology studies were provided in the original submission (stamp-dated 7/1/02) of NDA 21-519; the Sponsor relied upon the non-clinical studies that had been reviewed for and supported the approval of NDA 20-243 to support the current NDA. The non-clinical studies submitted under NDA 20-243 were determined to support approval of Luvox at that time (NDA 20-243 was approved on 12/5/94) contingent upon the Sponsor's (Phase IV) commitment to conduct repeat preclinical Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproduction studies in the rat, because the dosing in the original studies was considered inadequate.

In response to the initial submission of NDA 21-519 (stamp-dated 7/1/02), the Agency issued a letter (dated 9/5/02) requesting a rationale and justification for the selection of the proposed specifications for impurities/degradants in Luvox drug product that exceeded the 0.2% threshold for qualification of degradation products as described in the "Guidance for Industry-Q3B Impurities in New Drug Products." [This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27454), well after the approval of NDA 20-243 in 1994.]

The Sponsor addressed the issues raised by the Agency's 9/5/02 letter in a submission to NDA 21-519 (letter-dated 5/7/03), referring to (and resubmitting) an earlier submission (letter-dated 10/22/98) to NDA 20-243. Additionally, during the course of reviewing that submission, it was determined that specifications for several (other) impurities in drug substance had also been set above the threshold for qualification (as described in the "Guidance for Industry-Q3A Impurities in New Drug Substances;" 1996, revised in 2003). It was concluded that the impurity/degradant issues had not been adequately addressed.

1.2 AE letter addressed by the current submission.

On 2/9/04, the Agency issued an Approvable Letter for NDA 21-519 (and NDA 22-033) that included the following description of the Pharmacology/Toxicology issues that would need to be addressed before the NDA could be approved:

Pharmacology/Toxicology

The specifications set for a number of impurities are above the threshold for qualification in drug substance (i.e., above 0.15%) and/or drug product (i.e., above 0.2%). We recommend that you lower the specifications for these impurities to below the qualification threshold. If this is not possible, you need to qualify these impurities in the following studies (note exceptions below):

- a general toxicology study in one species, of 14-90 days duration;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]);
- an embryofetal development study in one species;
- a juvenile study in one species.

For the general toxicology, embryofetal development, and juvenile studies, justification should be provided for the species selected for each study.

Based on the information provided, we consider the addition product qualified for general toxicity in a 13-week study in rats and all but the [redacted] qualified in the embryofetal development study in rat (Study No. TX.114.07.05P). You indicated that there has been considerable human exposure to older formulations of fluvoxamine (possibly containing higher levels of one or more impurities) marketed (since late 1993) in several foreign countries. To the extent that you can provide documentation (i.e., actual levels of impurities rather than specifications) that the impurities have been qualified by this clinical use, no further testing of general toxicity would be needed.

With the exceptions noted, all the impurities with specifications set above the qualification threshold need to be qualified in the studies as listed above. These studies, except for the juvenile study, will be required prior to approval if the specifications cannot be lowered to below the qualification threshold.

The current submission (stamp-dated 5/17/06) addresses these issues and is reviewed below.

It should also be noted that in an amendment to the current NDA (stamp-dated 6/25/03), the Sponsor submitted study reports for Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicology studies in rats in support of the earlier Phase IV commitment (for NDA 20-243). Those reproductive toxicology studies have already been reviewed; the results were incorporated as revisions to the Impairment of Fertility and Pregnancy sections of labeling and provided to the Sponsor in the AE letter dated 2/9/04.

It should also be noted that the 2/9/04 AE letter included the following post-marketing commitment for juvenile animal studies, including qualification of relevant impurities/degradants in one species.

b(4)

Request for Post-marketing Study Commitment

We note that Luvox has not yet been evaluated in juvenile animals. Therefore, you need to conduct juvenile studies in rodent and non-rodent. The impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in one of these studies; the selection of species should be justified.

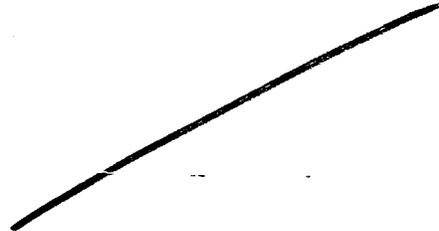
Appears This Way
On Original

Appears This Way
On Original

2.2 The Sponsor's response:

According to the current submission (attachment 12), the Sponsor identified impurities that would have required qualification:

b(4)



b(4)

These are the same we had identified (see table, above), plus the _____ by itself.

b(4)

In this submission, the Sponsor claimed to have reduced the specifications for _____ impurities _____ to levels that do not require qualification (however, this was not true; see discussion in section 2.3, below).

b(4)

They further claimed to have conducted 4 toxicology studies that would qualify the remaining 5 impurities, as summarized in the table, below.

Test:	Ames	Mouse Lymphoma TK Assay	14-Day General Toxicity	Embryo-Fetal Development	Juvenile Study
Impurity		X	X		X
	X	X			X
	X	X	X	X	X
	X	X	X		X
	X	X	X		X

b(4)

This submission contains reports for the 4 toxicology studies:

Appears This Way
On Original

On 10/2/06, we asked (via e-mail) the Sponsor to clarify the specifications for [REDACTED]. On 10/5/06, the Sponsor replied that there had been a miscommunication between their Pharmtox and Chemistry groups and that the specifications had not been lowered as claimed. They committed to tightening the specification for [REDACTED] in the drug substance. However, they could not lower the specification for [REDACTED] in the drug product; they committed to qualifying this degradant post-approval, with the studies to be completed within one year of approval. They felt that this was justifiable, because it is "a single related impurity, and the data show that as a degradant the [REDACTED] has most likely been in the marketed product and demonstrated many patient-years of favorable clinical experience." [The complete e-mail is included in the Appendix of this review.]

b(4)

We also asked (via e-mail on 10/13/06) the Sponsor whether they had submitted any Ames test that could serve to qualify the [REDACTED]. They replied (on 10/20/06) that "an earlier Ames study, study number H.114.496, was performed using test article containing [REDACTED]. There was no evidence of mutagenicity. The report was submitted to [REDACTED]. (They also re-submitted the report as an attachment to the e-mail.) Additionally, they plan to include the [REDACTED] in the Ames test they are proposing to conduct post-approval to qualify [REDACTED]. [The complete e-mail is included in the Appendix of this review.]

b(4)

The Ames test submitted to [REDACTED] is reviewed there and was found to be valid and negative; consequently, it can serve to qualify the [REDACTED].

b(4)

2.4 This Reviewer's conclusions:

The current specifications for the impurities/degradants of concern are provided in the table, below, with information on the studies that support qualification of each impurity/degradant.

[REDACTED] have been adequately qualified. The [REDACTED] has been adequately qualified, except for the Ames test, where it was present at only [REDACTED] rather than the [REDACTED] at which it is specified. [REDACTED] has only been qualified for embryo-fetal toxicity (as communicated in the AE letter). [REDACTED] has not been qualified in any of the 4 required tests and [REDACTED] has not been qualified in Ames test or chromosomal aberration test or for general toxicity.

b(4)

[The specification of [REDACTED] would result in exposure of patients to up to [REDACTED] of this impurity, compared with 0.6 mg at the threshold for qualification, at the 300-mg maximum recommended daily clinical dose. The specification of [REDACTED] for [REDACTED] would result in exposure of patients to up to [REDACTED] of this impurity, compared with 0.45 mg at the threshold for qualification, for the 300-mg maximum recommended daily clinical dose.]

b(4)

Table 2. Summary of the studies that would serve to qualify the specifications for impurities/degradants (above qualification thresholds) in drug substance (DS) and drug product (DP) as communicated in this submission.

IMPURITY/DEGRADANT	DS SPEC	DP SPEC	AMES TEST	CHROM AB	GENERAL TOX	SEG II
[REDACTED]						

b(4)

- 1: based on previous review of 13-month rat study.
- 2: based on 14-day study provided with this submission; [REDACTED]
- 3: based on previous review of Seg II study.
- 4: based on Seg II study provided with this submission, with [REDACTED]
- 5: based on MLA provided with this submission; [REDACTED] was also present at [REDACTED]
- 6: based on the Ames test provided with this submission; [REDACTED] was also present at [REDACTED]
- 7: based on an Ames test conducted in Japan in 1993 and provided to [REDACTED] in 1997 in [REDACTED] where it has been recently reviewed.

b(4)

Although not addressed in the formal submission, the Sponsor subsequently proposed (see e-mail in Appendix) qualifying [REDACTED] post-approval, with the studies to be completed within one year of approval. They felt that this was justifiable, because it is "a single related impurity, and the data show that as a degradant the [REDACTED] has most likely been in the marketed product and demonstrated many patient-years of favorable clinical experience."

b(4)

Appears This Way
On Original

3 COMMENTS ON THE LITERATURE REFERENCE PROVIDED BY THE SPONSOR SHOWING FLUVOXAMINE-INDUCED HYPOGLYCEMIA IN MICE:

_____ The Medical Officer (Dr. Gregory Dubitsky) reviewing this NDA asked Pharmacology/Toxicology to comment on the single literature reference for a non-clinical study that _____

b(4)

_____. The reference is for Yamada and coworker's report (Eur J Pharmacol 382:211-215, 1999) where they demonstrated that an ip dose of 10 or 20 mg/kg, but not 5 mg/kg, to male ddY mice resulted in a rapid, but transient increase in plasma glucose: maximally increased (less than 40% higher than control) at 15 min (the earliest time point measured) and back to baseline by 1 hr (the latest time point measured). A similar pattern was seen at the same doses of fluoxetine, whereas maprotiline did not alter glucose levels at those doses over that time range. The systemic exposure to fluvoxamine (or any of the drugs) was not determined.

Because the route used in this single-dose study (intraperitoneal injection) is not the same route to be used clinically (oral) and the hypoglycemia was so slight and so short-lived, it seems unlikely that this finding is relevant to clinical usage. The non-clinical studies that supported the original approval of Luvox did not appear to indicate problems of glucose regulation. If there is concern about the possibility of hypoglycemia with fluvoxamine maleate, the Sponsor should further investigate this finding, in humans (and/or animals).

Appears This Way
On Original

Appears This Way
On Original

4 OVERALL CONCLUSIONS:

In response to the original submission of this NDA, the Division issued an Approvable letter (dated 2/9/04), with approval based in part on the Sponsor's adequately addressing our concerns about specifications for several impurities that had been set above the threshold for qualification in drug substance (i.e., above 0.15%) and/or drug product (i.e., above 0.2%). The Sponsor was asked to lower the specifications if possible or to qualify them in the following non-clinical studies: 1) a general toxicology study in one species, of 14-90 days duration; 2) *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); 3) an embryo/fetal development study in one species; and 4) a juvenile animal study. All qualification studies, except the juvenile study, were required prior to approval.

In the current submission (the response to our AE letter), the Sponsor provided reports for 4 studies to help qualify these impurities/degradants. In a communication during this review cycle, the Sponsor also informed us that the [redacted] was qualified at [redacted] in an Ames test that had been previously submitted to the [redacted]. Based on this new information, in combination with the studies that had previously been submitted (and reviewed under the original submission), the [redacted] have been adequately qualified. The [redacted] has been adequately qualified, except for the Ames test, where it was present at only [redacted], rather than the [redacted] at which it is specified. [redacted] was considered to be qualified in a previously submitted embryo-fetal development study (as communicated in the AE letter), but not in any other studies (viz., for genotoxicity or general toxicity).

b(4)

However, [redacted] (which is specified at [redacted] in the drug product) has not been qualified in any of the 4 required tests and [redacted] (which is specified at [redacted] in the drug substance) has not been qualified in Ames test or chromosomal aberration test or for general toxicity.

b(4)

According to the ICH Guidances for Impurities in New Drug Substances (Q3A) or New Drug Products (Q3B), impurities or degradation products "that are also significant metabolites present in animal and/or human studies are generally considered qualified." The Sponsor has not suggested that either [redacted] (or any other impurity) is a metabolite of fluvoxamine. Additionally, this Reviewer was unable to find any documentation indicating that either [redacted] is a metabolite of fluvoxamine, much less "a significant metabolite," in either animals ("Fluvoxamine: Metabolic fate in animals," Ruijten, H.M, et al., Drug Metab Dispo 12(1):82-92, 1984) or humans ("Fluvoxamine maleate: Metabolism in man," Overmars, H, et al., Eur J Drug Metab & Pharmacokin 8(3):269-280, 1983). [redacted]

b(4)

In this submission, the Sponsor claimed to have lowered the specifications for both _____, so that they would not require qualification, however, this was not true. When questioned, the Sponsor explained that there had been a miscommunication between their PharmTox and Chemistry teams and the specification for _____ in the drug product could not be lowered below _____ however, it had not been included in the currently submitted qualification studies. In several communications with the Chemistry Reviewer during this review cycle, the Sponsor has claimed an intention to lower the specification for _____ but has not yet done so.

b(4)

The Sponsor has proposed to qualify _____ as a post-marketing commitment (and to [adequately] qualify the _____ in the Ames test proposed for qualification of _____ post-marketing). The Sponsor suggested that post-marketing qualification of _____ is justifiable, because it is "a single related impurity, and the data show that as a degradant the _____ has most likely been in the marketed product and demonstrated many patient-years of favorable clinical experience." This Reviewer does not find this argument compelling, because most of the studies required for qualification assess toxicities that are not adequately addressed in humans, either in clinical studies or post-marketing, namely the 2 genotoxicity studies (as surrogates for carcinogenicity) and the reproductive toxicity study (as a test for effects on embryo-fetal development). If actual evidence were provided that the levels of this degradant in drug product that had been marketed were at least as high the currently-proposed specification, a repeated dose general toxicity study would not be required for qualification.

b(4)

It is this Reviewer's opinion that _____ should be qualified prior to approval, as communicated in the AE letter, because its specification in the (current IR) drug product is substantially greater than _____ the threshold for qualification and is higher _____ for the CR product that is currently under review (under NDA 22-033; also sponsored by Solvay).

b(4)

_____ is currently specified at _____ in the drug substance, which is just slightly _____ above the threshold for qualification of 0.15%. Although the Sponsor has not yet lowered the specification of _____ in drug substance so that it will not require qualification (i.e., from _____ to 0.15%), it seems that the Sponsor is able and should be required to do so. If the specification for this impurity cannot be lowered, qualification will be required for genotoxicity and general toxicity; this impurity has already been qualified for embryo-fetal toxicity (as communicated in the AE letter).

b(4)

In conclusion, it is this Reviewer's opinion that all impurities with specifications above the threshold for qualification in either the drug substance or drug product, specifically _____ should be adequately qualified prior to drug approval, as was communicated to the Sponsor in the (2/9/04) AE letter.

b(4)

5 RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, this NDA is **APPROVABLE**, if qualification issues for 2 impurities/degradants are adequately addressed.

Based on new information provided in the current submission, in combination with the studies that had previously been submitted (and reviewed under the original submission), several of the impurities/degradants that were of concern have been qualified.

It should be noted that although the [redacted] is considered to be adequately qualified for the current specification of [redacted] in drug substance and product, it was present at only [redacted] in the Ames test. [It should be noted that the specification for this impurity has been set higher [redacted] for the CR formulation of this drug, which is currently under review under NDA 22-033. Qualification at [redacted] in the Ames test will not be considered adequate for that higher specification of [redacted] in the CR formulation.]

b(4)

The degradant [redacted] which has been specified at [redacted] in the drug product (with a threshold for qualification of 0.2%), still has not been qualified. In the current submission (their response to our AE letter), the Sponsor clearly recognized the need to either lower the specification or qualify this degradant. However, they subsequently informed us that neither of these options was accomplished, because of a miscommunication between the PharmTox and Chemistry groups within their company. Based on information from that communication from the Sponsor and Dr. David Claffey's CMC review of this submission, it appears that this specification for [redacted] cannot be lowered. Consequently, [redacted] will need to be qualified and this should be done prior to approval as was communicated in the AE letter (dated 2/9/04). [It should also be noted that the specification for this degradant has been set higher [redacted] for the CR formulation of this drug, which is currently under review under NDA 22-033.]

b(4)

Additionally, the Sponsor should lower the specification for [redacted] in the drug substance from [redacted] (their previously proposed specification) to 0.15% (the threshold for qualification), as they have stated that they would. If this cannot be accomplished, this impurity should be qualified, also prior to approval as was communicated in the AE letter (dated 9/24/04). It should be noted that this impurity is considered qualified for embryo-fetal toxicity (as communicated in the AE letter). [In their response to our AE letter, the Sponsor claimed to have lowered the specification for this impurity, but subsequent communications with the Sponsor have failed to obtain their revised specification.]

b(4)

Finally, the Sponsor should be reminded of the post-marketing requirement regarding juvenile animal studies. In the previous AE letter (dated 2/9/04), we asked for juvenile studies in 2 species:

"To support the use of Luvox in children, juvenile studies in 2 animal species (rat and dog) need to be conducted; this may be done after approval. The impurities should be qualified in 1 of these studies."

However, our thinking on animal juvenile studies has evolved and we will now only request a single juvenile study, in rats, for fluvoxamine maleate; based on extensive pre- and post-marketing experience in adults, the non-clinical studies that supported approval for use in adults, and the pre- and post-marketing experience in children and adolescents aged 8-17 (under the original NDA 20-243 and several generics). [Based on the original review of the 7-month and 1-year repeated-dose general toxicity studies in dogs, under NDA (that supported NDA 20-243), which were conducted at MTDs, there was no evidence of toxicity in the heart or sex organs, toxicities that might not be adequately assessed in rodents.]

b(4)

It should be noted that the Phase IV commitment for NDA 20-243, to conduct repeat Segment I (mating and fertility) and Segment II (embryo/fetal development) reproductive toxicology studies in rats, using adequate doses, was previously determined to have been fulfilled by the studies provided to the original submission of NDA 21-519. Revised labeling, incorporating the results of those studies, including decreased fertility, litter size, and fetal weight and increased fetal abnormalities (specifically, folded retinas), was communicated to the Sponsor in the previous AE letter (2/9/04).

Appears This Way
On Original

Appears This Way
On Original

6 INFORMATION TO BE COMMUNICATED TO THE SPONSOR:

PHARMACOLOGY/TOXICOLOGY APPROVABILITY ISSUES:

The specification for [REDACTED] in the drug product is set at [REDACTED] which is above the threshold for qualification (i.e., above 0.2%). Because it appears that you are unable to lower this specification, you will need to qualify this impurity/degradant in the following studies prior to approval:

b(4)

- a general toxicology study in one species, of 14-90 days duration; or demonstrate prior human exposure;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and
- an embryofetal development study in one species.

The specification for [REDACTED] in the drug substance is set at [REDACTED] which is above the threshold for qualification (i.e., above 0.15%). You have indicated that you intend to lower this specification, but have not provided us with documentation of your revised specification. Such documentation or qualification of this impurity in the studies listed above will be needed prior to approval. If qualification is required, this impurity is currently considered to be qualified for embryo-fetal toxicity, but not for genotoxicity or general toxicity, as communicated in our previous AE letter (dated 2/9/04).

b(4)

Although the [REDACTED] is considered to be adequately qualified for the current [REDACTED] specification in drug substance and product, the [REDACTED] level of this impurity in the Ames test will not be adequate to qualify specifications higher than [REDACTED]

b(4)

PHARMACOLOGY/TOXICOLOGY POST-MARKETING COMMITMENT:

We note that Luvox has not yet been evaluated in juvenile animals. Although we previously requested (in our Approvable letter dated 2/9/04) that you conduct juvenile studies in rodent and non-rodent, our thinking on juvenile studies has evolved and we will only require a juvenile study in the rat. As previously communicated (in our Approvable letter dated 2/9/04), the impurities present in drug substance and/or drug product at levels above the thresholds for qualification should be tested in this study.

Appears This Way
On Original

7 LABELING:

Revised labeling is not being provided at this time. However, the following comments should be communicated to the Sponsor:

- Under CLINICAL PHARMACOLOGY/ Pharmacodynamics, if you want to change labeling to _____ you will need to resubmit the studies that support those claims. **b(4)**
- Under PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility/Carcinogenicity, the first sentence _____ should be deleted, based on the revised labeling for Impairment of Fertility and Pregnancy sections. We neglected to remove this sentence in the labeling communicated in the previous AE letter (2/9/04). **b(4)**
- Under PRECAUTIONS: Impairment of Fertility and Pregnancy/Teratogenic Effects sections, the route of dosing (oral) should be included. We neglected to include this in the labeling communicated in the previous AE letter (2/9/04).

Appears This Way
On Original

Appears This Way
On Original

8 SIGNATURES

Linda H. Fossom, Ph.D., Reviewing Pharmacologist *{see appended electronic signature page}*

Barry Rosloff, Ph.D., Supervisory Pharmacologist *{see appended electronic signature page}*

9 APPENDICES:

Appears This Way
On Original

Appears This Way
On Original

9.1 Communication with the Sponsor regarding their failure to lower specifications for [REDACTED]

b(4)

From: Horton, Rex [mailto:Rex.Horton@solvay.com]
Sent: Thursday, October 05, 2006 3:37 PM
To: Bender, William
Cc: Tian, Judy
Subject: RE: NDA 21,519

Dear Dr. Bender,

The specifications for drug substance were never tightened as communicated in the pharm/tox response. Solvay does commit to tightening the specifications for [REDACTED] in the drug substance. An updated drug substance specification is being prepared and will be submitted as an amendment to the application.

b(4)

However, due to a miscommunication/error between our internal pharm/tox experts and cmc groups, the qualifying toxicity studies were not performed using the [REDACTED] and the drug product specifications cannot be tightened for [REDACTED]; based on our review of the stability data and the historical performance of the drug product. Prior to initiation of the toxicity qualification studies, it had been communicated internally that we could tighten the specs for [REDACTED] but this was most likely based on a review of drug substance data only. Therefore, [REDACTED] was removed from initial plans to conduct the studies with a percentage [REDACTED] for qualification.

b(4)

Solvay does, however, now commit to performing appropriate qualification of the impurity. We will immediately begin planning for the studies and will submit proposed study designs for your review; we will then execute and complete the required studies within one year post-approval of the application to qualify the level of [REDACTED] at the previously approved level. Solvay concludes that post-approval submission is appropriate because this is a single related impurity, and the data show that as a degradant the [REDACTED] has most likely been in the marketed product and demonstrated many patient-years of favorable clinical experience.

b(4)

If you have any questions regarding this response or need further information, please contact myself or Judy Tian at the numbers provided below or via e-mail.

Best Regards,

Rex Horton
Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062
(770) 578-5846 phone
(404) 547-2685 cell
(770) 578-5864 fax

From: Tian, Judy
Sent: Monday, October 02, 2006 8:10 AM
To: Horton, Rex

Cc: Ruggirello, Don
Subject: FW: NDA 21,519

Rex:

Please see the email from FDA.

Kind Regards,

Judy Tian

*Assistant Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Rd.
Marietta, GA 30062
(Tel) (770)578-5782
(Cell) (678)468-6405
(Fax) (770)578-5864
email: judy.tian@solvay.com*

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Monday, October 02, 2006 8:02 AM
To: Tian, Judy
Cc: Grewal, Renmeet
Subject: NDA 21,519

Good Morning Judy,

In your submission dated 5/16/06 to NDA 21-519 for fluvoxamine maleate tablets (Luvox), you indicated that the specifications for some impurities, namely _____ had been lowered enough so that they do not require toxicological qualification. However, based on information in that submission, _____ appears to be still specified at NMT _____ in the drug product, which is above the qualification threshold of 0.2% (although the specification of 0.15% in the drug substance meets the threshold for drug substance) and _____ appears to be still specified at NMT _____ in drug substance, which is above the threshold of 0.15%.

b(4)

If the specifications cited above are not the ones you intended, please indicate to us where we can find the correct specifications or submit them to us as soon as possible.

Thank you,
William H. Bender
LCDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

9.2 Communication with the Sponsor regarding Ames test(s) that could serve to qualify the [REDACTED] of fluvoxamine. [This e-mail from the Sponsor also included 1) the report for study H.114.496; and 2) a table comparing analyses of some batches of fluvoxamine maleate, including the one used in the Ames test of interest (see next section of this Appendix).]

b(4)

From: Regulatory Submissions [mailto:Regulatory.Submissions@solvay.com]
Sent: Friday, October 20, 2006 12:53 PM
To: Bender, William
Cc: Grewal, Renmeet
Subject: FW: NDA 21,519

This message is sent on behalf of Judy Tian, Assistant Director, Regulatory Affairs.

Bill:

This information is regarding your question dated October 13, 2006 and our Response to Approvable submission dated 5/16/06 to NDA 21-519, on the subject of Ames testing of the [REDACTED] impurity. In addition to the recent Ames testing of the impurities, an earlier Ames study, study number H.114.496, was performed using test article containing [REDACTED]. There was no evidence of mutagenicity. The report was submitted to [REDACTED] on May 5, 1997. However, as you requested, we are re-submitting the report as an attachment to this email.

b(4)

As discussed in our correspondence last week, Ames testing will also be included in tests to be performed to qualify the level of [REDACTED] in the drug product. As part of this testing we will also re-test the [REDACTED].

b(4)

Please let me know if you have any questions.

Kind Regards,

Judy Tian

*Assistant Director, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Rd.
Marietta, GA 30062
(Tel) (770)578-5782
(Cell) (678)468-6405
(Fax) (770)578-5864
email: judy.tian@solvay.com*

Please respond to Judy Tian, Assistant Director, Regulatory Affairs at the following email address: Regulatory.Submissions@solvay.com

NDA 21-519 (N-000, AZ, stamp-dated 5/17/06): Response to AE Letter dated 2/9/04.
Pharmacologist Review.

page 25

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Friday, October 13, 2006 2:17 PM
To: Tian, Judy
Cc: Horton, Rex; Grewal, Renmeet
Subject: NDA 21,519

Good Afternoon,

Regarding your Response to Approvable submission dated 5/16/06 to NDA 21-519 for fluvoxamine maleate tablets (Luvox), the Ames test that you provided to qualify several impurities contained only [REDACTED] compared with the specification of NMT [REDACTED] for this impurity in the drug substance and the drug product. If you have conducted another Ames test that could serve to qualify the fluvoxamine [REDACTED], please indicate where/when the study report was submitted or, preferably, resubmit the study report.

b(4)

Thank you,
William H. Bender
LCDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Pharm/Tox- 1

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Fossom
11/13/2006 05:14:51 PM
PHARMACOLOGIST

Barry Rosloff
11/14/2006 10:59:47 AM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 2/9/04

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 21-519

Based upon review of the nonclinical data submitted to NDA 21-519 (Review and Evaluation of Pharmacology/Toxicology Data, 2/6/04), Dr. Fossom recommends that (1) a series of impurities, for which specifications have been set above the threshold for qualification, need to be qualified prior to approval and (2) juvenile studies in rodent and nonrodent will be needed postapproval. I concur with these recommendations, with one exception.

Dr. Fossom recommends that the [redacted] impurities which are solely process impurities (i.e., [redacted]) need to be qualified only in *in vitro* genotoxicity studies (i.e., *in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]). It is Dr. Fossom's opinion that the specification for these [redacted] impurities is "only slightly above the qualification threshold [redacted] vs 0.15%", and this small difference mitigates the need for qualification in general toxicity, embryofetal development, and juvenile studies. Also, Dr. Fossom points out that two of these [redacted] impurities, i.e., [redacted] have been qualified in an embryofetal development study.

b(4)

This recommendation is certainly not unreasonable. However, the specification set for these [redacted] impurities are above the qualification threshold, and it is difficult to make distinctions regarding the need or lack thereof for qualification depending on the degree to which the qualification threshold has been exceeded. Therefore, based on all information available (cf. Memo to File: DMF [redacted] 2/9/04), I am recommending that, to the extent that these impurities have not been qualified in the studies listed in Dr. Fossom's review, they need to be so.

b(4)

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lois Freed
2/9/04 01:25:01 PM
PHARMACOLOGIST

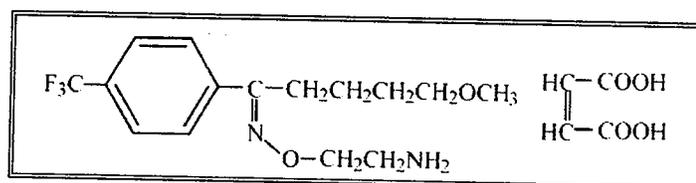
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
 Division Name: Neuropharmacological Drug Products
 HFD# 120
 Review Completion Date: February 6, 2004.

Review number: 1.
 NDA number: 21-519.
 Serial number/date/type of submission: N-000, 4T / June 23, 2003 / non-clinical toxicology.
 Information to sponsor: Yes (X) No ()
 Sponsor: Solvay Pharmaceuticals.
 Manufacturer for drug substance: same.

Drug:

Code Name: not provided.
 Generic Name: fluvoxamine maleate.
 Trade Name: Luvox.
 Molecular Formula / Molecular weight: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ / 434.41.
 USAN Name: 5-methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate.
 Structure:



Relevant INDs/NDAs/DMFs: NDA 20-243 (previously approved, but withdrawn; sponsored by Solvay Pharmaceuticals, Inc); DMF (describing manufacture of drug substance; held by Solvay Pharmaceuticals, Inc); also see Appendix to this review.

b(4)

Drug Class: Selective serotonin reuptake inhibitor (SSRI).

Indication: Obsessive-Compulsive Disorder (OCD).

Clinical formulation: tablets; 25, 50, and 100 mg strengths.

Route of administration: oral.

Proposed clinical Use: For the treatment of Obsessive-Compulsive Disorder (OCD). According to the Sponsor's draft labeling, Luvox will be used in adult and pediatric populations: in adults, starting at 50 mg, with a maximum recommended daily dose of 300 mg; in children and adolescents, starting at 25 mg, with maximum recommended daily dose of 200 mg for children up to age 11 and 300 mg for adolescents.

Previous clinical experience: Luvox was approved for treatment of Obsessive-Compulsive Disorder under NDA 20-243 (12/5/94) and marketed by Solvay until 9/24/97. Several (12) generic formulations of Luvox have been approved in the US in 2000-2002. Luvox is currently approved in several other countries.

Disclaimer: Where feasible, the Sponsor's figures and tables were incorporated directly into this review and noted as such.

Introduction and drug history: Luvox (sponsored by Solvay) was approved for treatment of Obsessive-Compulsive Disorder (OCD) under NDA 20-243 on 12/5/94. Luvox was marketed by Solvay until 9/24/97, when it was put under Application Integrity Policy (AIP) for chemistry irregularities. In an agreement with the Agency, Solvay withdrew NDA 20-243 (on 5/13/02) and submitted a new NDA for Luvox (the current NDA 21-519) on 7/1/02. Because the AIP was not lifted until 4/9/03, the primary goal date for review of NDA 21-519 is 2/9/04 (10 months from the date when the AIP was lifted), although the original submission of this NDA was stamped 7/1/02.

No non-clinical pharmacology or toxicology studies were provided in the original submission (dated 7/1/02) of NDA 21-519; the Sponsor relied upon the non-clinical studies that had been reviewed for and supported the approval of NDA 20-243 to support the current NDA. The non-clinical studies submitted under NDA 20-243 were determined to support approval of Luvox at that time (NDA 20-243 was approved on 12/5/94) contingent upon the Sponsor's (Phase IV) commitment to conduct repeat preclinical Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproduction studies in the rat, because the dosing in the original studies was considered inadequate. In an amendment to the current NDA (dated 5/7/03), the Sponsor submitted study reports for Segment I and Segment II reproductive toxicology studies in support of that Phase IV commitment. These reproductive toxicology studies are reviewed below and the results included in revised labeling; the Sponsor's draft labeling (provided 4/16/03 in the resubmission of the original NDA to the Electronic Document Room) did not include this new information.

In response to the initial submission of NDA 21-519 (on 7/1/02), the Agency issued a letter (dated 9/5/02) requesting a rationale and justification for the selection of the proposed specifications for impurities/degradants in Luvox drug product that exceeded the 0.2% threshold for qualification of degradation products as described in the "Guidance for Industry-Q3B Impurities in New Drug Products." [This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27454), well after the approval of NDA 20-243 in 1994.] The Sponsor addressed the issues raised by the Agency's 9/5/02 letter in a submission to NDA 21-519 (letter-dated 5/7/03); this response by the Sponsor is reviewed below. [During the course of this review, it was determined that specifications for several impurities in drug substance had also been set above the threshold for qualification (as described in the "Guidance for Industry-Q3A Impurities in New Drug Substances;" 1996, revised in 2003).]

Studies within this submission: No non-clinical pharmacology or toxicology studies were provided in the original submission (initially submitted on 7/1/02 and resubmitted to the Electronic Document Room on 4/16/03).

Two subsequent submissions to the NDA are relevant to non-clinical Pharmacology/Toxicology:

1. A Pharmacology/Toxicology amendment (submitted to the Electronic Document Room 6/20/03) pertaining to the Sponsor's Pharmacology/Toxicology Phase IV commitment for Luvox under NDA 20-243; this submission is addressed in Section 1 of this review, which deals with reproductive toxicology studies submitted in fulfillment of the Phase IV commitment.
2. A response (submitted to the Electronic Document Room 5/7/03) to the Agency's letter dated 9/5/02; this submission is addressed in Section 2 of this review, which deals with impurities/degradants in drug substance and drug product.

Studies not reviewed within this submission: none.

Appears This Way
On Original

Appears This Way
On Original

EXECUTIVE SUMMARY

1. Recommendations:

1.1 Recommendations on approvability: Approvable.

1.2 Recommendations for non-clinical studies: Several impurities in drug substance and/or drug product had specifications above thresholds for qualification. If the specifications for these impurities cannot be lowered below the threshold(s), the impurities will need to be qualified. A list of the studies required to qualify these impurities is provided in the Section 3, OVERALL CONCLUSIONS AND RECOMMENDATION at the end of this review.

1.3 Recommendations on labeling: The results of the repeat reproductive toxicology studies (see section 2.1, below) will need to be added to labeling. Revised labeling is provided in Section 1.6 in the body of this review.

2. Summary of non-clinical findings:

2.1 Brief overview of non-clinical findings: This NDA relies upon the non-clinical studies that supported the approval of fluvoxamine maleate for the treatment of Obsessive-Compulsive Disorder under NDA 20-243. The approval of NDA 20-243 was contingent upon a Phase IV commitment to repeat the Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicity studies in rats; the doses in the original studies were considered to have been inadequate. The Sponsor provided these repeat studies in the current NDA. Review of these repeat studies determined that they are acceptable to fulfill the Phase IV commitment to NDA 20-243. The high dose (i.e., 240 mg/kg) was justified based upon deaths at higher doses in dose range-finding studies and maternal and paternal toxicity (deaths and decreased body weights) in the repeat studies; the high dose used in the repeat studies was 3-times the high dose used in the original studies (i.e., 80 mg/kg). In the original studies, no effects were seen on fertility or pregnancy parameters. The higher doses used in the repeat Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicology studies decreased fertility, litter size, and fetal weight and increased fetal abnormalities (specifically, folded retina(s)).

Additionally, the specifications for several — impurities in clinical drug substance and/or drug product are above the thresholds for qualification. From the information available to the current NDA, it appears that these impurities have not been fully qualified (see Section 2.3 in the body of this review for the details of the evidence that partially qualifies some of the impurities).

b(4)

2.2 Pharmacologic activity: Fluvoxamine maleate (Luvox) is a selective serotonin reuptake inhibitor (SSRI).

2.3 Non-clinical safety issues relevant to clinical use: At the higher doses used in the repeat Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicology studies, doses that decreased fertility, litter size, and fetal

weight and that increased fetal abnormalities (specifically, folded retina(s)) were achieved in rats.

Additionally, the specifications for several — impurities are above the threshold for qualification in drug substance and/or drug product; these impurities have not been adequately qualified in the current NDA.

b(4)

Appears This Way
On Original

Appears This Way
On Original

TABLE OF CONTENTS

1	REPRODUCTIVE TOXICOLOGY: SUBMITTED IN FULFILLMENT OF A PHASE IV COMMITMENT FOR NDA 20-243.....	1
1.1	BACKGROUND FOR THE PHASE IV COMMITMENT:.....	1
1.2	DOSE-RANGE FINDING STUDIES:.....	1
1.3	SEGMENT I STUDY IN RATS: FERTILITY AND EARLY EMBRYONIC DEVELOPMENT	4
1.4	SEGMENT II STUDY IN RATS: EMBRYO-FETAL DEVELOPMENT.	10
1.5	SUMMARY AND CONCLUSIONS FOR REPRODUCTIVE TOXICITY STUDIES:.....	13
1.6	LABELING:	15
2	IMPURITY AND DEGRADANT ISSUES:.....	17
2.1	HISTORY/BACKGROUND:	17
2.2	CURRENT STATUS:.....	18
2.3	SUMMARY AND CONCLUSIONS FOR IMPURITY ISSUES:.....	22
3	OVERALL CONCLUSIONS AND RECOMMENDATIONS:	24
4	SIGNATURES.....	25
5	APPENDIX:.....	26

1 REPRODUCTIVE TOXICOLOGY: SUBMITTED IN FULFILLMENT OF A PHASE IV COMMITMENT FOR NDA 20-243.

1.1 Background for the Phase IV commitment:

Luvox (fluoxetine maleate) was approved on 12/5/94 under NDA 20-243 (sponsored by Solvay Pharmaceuticals) for the treatment of Obsessive-Compulsive Disorder (OCD). The conditions of that approval included reference to the Sponsor's Phase IV commitment "...to conduct repeat preclinical Segment I and II reproduction studies in the rat based upon ...rangefinding and/or toxicokinetic studies. We [The Division] believe[d] that the original studies did not achieve adequate exposure." This was also described in the Approvable letter, issued 8/30/94. The Approval letter also noted that this drug would be considered Pregnancy Category C, because of decreased pup weights and survival in the Segment III reproduction study in rats. _____

b(4)

In an amendment to the current NDA (dated 5/7/03), the Sponsor submitted study reports for Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicology studies in rats in support of that Phase IV commitment. These reproductive toxicology studies are reviewed below.

It should be noted that the labeling that was submitted (Electronic Document Room submission dated 4/16/03) by the Sponsor for "Impairment of Fertility" and for "Pregnancy" appear to be from the original studies: Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) studies in rats at up to 80 mg/kg/day (i.e., 2 times the maximum human daily dose on a mg/m² basis) and Pregnancy Category C.

1.2 Dose-range finding studies:

- **Mating and fertility dose range-finding study in male rats** (Solvay's report no. TX.114.07.04P CRO; _____ study no. 4019-001PR; volume 1, pages 3-297): male _____ CD®(SD)IGS BR VAF/Plus®) rats (8/group) were dosed with 0, 160, 240, 320, or 400 mg/kg (10 ml/kg; lot no. 35572) by oral gavage for 28 days prior to and during mating with untreated females, females were examined for corpora lutea, implantation sites, uterine contents at GD13. **Paternal variables: deaths at 320 mg/kg** (2/8, similar to deaths at 400 mg/kg, except 1 had dark red lungs and slightly dilated renal pelvis at necropsy) **and 400 mg/kg** (4/8; 2 sacrifice on day 7, 1 found dead on day 8, another on day 12; all had all normal tissues at necropsy, with clinical signs, such as red perioral substance, excess salivation, chromorhinorrhea, ungroomed coat, urine-stained abdominal fur, etc, and decreased body weights); dose-related centrilobular hepatocellular hypertrophy at all doses; scattered large foamy (alveolar) macrophages in 1/8 at 240mg/kg, and

b(4)

all rats at higher doses; decreased body weights; increased ALP (↑29% at 320, 60% at 400), potassium (↑20% at 320, 25% at 400), BUN (↑29% at 320 and 400); decreased glucose (↓30% at 400), cholesterol (↓35% at 160, ~58% at 24 and 320, 66% at 400); **Fertility variables:** increased number of days of pairing before mating at ≥240 mg/kg (2.4 days in controls, and LD, 4.5 d at 240, 5.7 d at 320, 7.2 d at 400), all males mated with first female within 7 days, decreased pregnancy/mating ratio at ≥240 mg/kg.

NB This report notes that when doses of 0, 240, 320, 480, and 640 were administered (10 ml/kg, at pH 2.0) in a pilot study, 8/8 male rats at 640 and 5/8 male rats at 480 mg/kg died within 9 days of start of dosing.

TK was calculated for day 1 and final day of dosing in satellite rats (Solvay's study report TX.114.07.08 CRO, ██████ report no. QKAN-2001-0195-ADM, volume 1, pages 298-349): samples (drawn 0.5, 1, 2, 4, 12, and 24 hr after dosing on days 1 and last day of co-habitation; 6 rats/dose, 2 rats/time point) were analyzed for fluvoxamine. Results were adequate to verify drug administration, but exposure (Cmax, AUC) calculations were not very reliable, due to the small sample size (i.e., only 2 rats per time point). Nonetheless, the exposures appeared to be increasing with dose (see table, below).

b(4)

Table 1. Systemic exposures in male rats administered fluvoxamine maleate for 4-5 weeks. [Sponsor's table, excerpted directly from volume 1, page 305, of this submission.]

Dosage: ^a	Day 1				Day Last			
	160	240	320	400	160	240	320	400
Cmax (ng/mL)	986	1031	994	2774	955	1490	1670	3707
AUClast (ng•hr/mL) ^{b,c}	8411	14578	17659	31267	8920	23388	25603	53854

a: Dosages are expressed in mg/kg/day.
 b: AUClast is the area under the plasma drug concentration time curve calculated from 0-24 hours.
 c: AUClast for the 160 mg/kg/day regimen is calculated from 0-12 hours.

- **Mating and fertility dose range-finding study in female rats** (Solvay's report no. TX.114.07.3P CRO; ██████ study no. 4019-002PR; volume 1, pages 350459, volume 2, pages 460-622): virgin female ██████ :CD®(SD)IGS BR VAF/Plus®) rats (8/group) were dosed with 0, 160, 240, 320, or 400 mg/kg (10 ml/kg; lot no. 35261) by oral gavage for 14 days prior to and during mating with untreated male breeders, and through GD 17; females were examined for corpora lutea, implantation sites, uterine contents at GD21; **Maternal variables: deaths at 320 mg/kg** (1/8, moribund sacrifice on GD 9, with signs similar to deaths at 400

b(4)

mg/kg, except 1 had dark red lungs and slightly dilated renal pelvis at necropsy) **and 400 mg/kg** (4/8; 3 found dead on days 6, 9, and 16, 1 moribund sacrificed on day 7; most had all normal tissues at necropsy (except small spleen in 1); all had lost weight from beginning of dosing; common clinical signs included perioral substance, excess salivation, chromorhinorrhea, ungroomed coat, urine-stained abdominal fur, etc, and decreased body weights); At higher doses of 320 and 400 mg/kg, lung histopathology: scattered large foamy (alveolar) macrophages; dose-dependent decreased body weights and weight gains at ≥ 240 mg/kg for 1st week of dosing only, but also during gestation; increased BUN ($\uparrow 29\%$ at 320 and 400); decreased total protein ($\downarrow 30\%$ at 400), albumin ($\downarrow 35\%$ at 160, $\sim 58\%$ at 24 and 320, 66% at 400), and globulin ($\downarrow 35\%$ at 160, $\sim 58\%$ at 24 and 320, 66% at 400); **Fertility variables: decreased number of estrus stages** during pre-mating period at ≥ 320 mg/kg; no apparent effect on number of days of pairing before mating, all females mated with first male; **decreased litter means for implantations, litter size, and fetal body weights** at ≥ 240 mg/kg; **increased resorptions** at ≥ 160 mg/kg.

NB The study reports notes that when doses of 0, 240, 320, 480, and 640 were administered (10 ml/kg, at pH 2.0) in a pilot study, 8/8 female rats at 640 and 5/8 female rats at 480 mg/kg died within 9 days of start of dosing.

TK was calculated on 1st and last days of dosing in satellite rats (Solvay's study report TX.114.07.07 CRO, ~~report no.~~ report no. QKAN-2001-0194-ADM, volume 2, pages 623-674): samples (drawn 0.5, 1, 2, 4, 12, and 24 hr after dosing on days 1 and last day of co-habitation; 6 rats/dose, 2 rats/time point) were analyzed for fluvoxamine. Results were adequate to verify drug administration, but exposure (C_{max}, AUC) calculations were not very reliable, due to the small sample size (i.e., only 2 rats per time point). Nonetheless, the exposures appeared to have plateaued at doses ≥ 320 mg/kg (see table, below).

b(4)

Table 2. Systemic exposures in female rats administered fluvoxamine maleate for 4-5 weeks. [Sponsor's table, excerpted directly from volume 2, page 630, of this submission.]

Table 3								
Mean Pharmacokinetic Parameters Calculated from Plasma Concentrations of Fluvoxamine								
Dosage:	Day 1				GD 17			
	160	240	320	400	160	240	320	400
C _{max} (ng/mL)	650	1382	1379	1402	1472	1893	3551	1993
AUC _{last} (ng·hr/mL) ^a	7019	21375	21456	19131	ND ^b	31936	42239	40018

a: AUC_{last} is the area under the plasma drug concentration time curve calculated from 0-24 hours.
b: ND: not determined.

1.3 Segment I study in rats: Fertility and early embryonic development

Study title: Oral (gavage) fertility and general reproduction toxicity study of fluvoxamine maleate in rats.

Key study findings:

- At doses of 0, 60, 120, and 240 mg/kg, both males and females dosed;
- NOAEL was 60 mg/kg for general fertility (increased number of days of cohabitation until mating and decreased resulting pregnancies at 120 mg/kg);
- NOAEL was 60 mg/kg for fertility of males (↓ sperm count and ↓ epididymis weight at ≥120 mg/kg); NOAEL was 120 mg/kg for toxicity (1 HD male was sacrificed moribund at 240 mg/kg);
- NOAEL was 120 mg/kg for fertility of females (tendency for decreased number of implantations and viable and non-viable embryos; and increased ovary weights at 240 mg/kg); no limiting toxicity determined in this study.

Study no.: TX.114.07.06P CRO.

Volume #, and page #: volume 2, pages 675-887, and volume 3, pages 888-1209.

Conducting laboratory and location: _____

Date of study initiation: dosing male rats (28 days before cohabitation and through 21-day cohabitation) 3/27-5/17/01; dosing female rats (15 day before cohabitation and through GD7) 4/9-5/21/01.

GLP compliance: yes, see page 1206.

QA reports: yes, see pages 1208-1209.

Drug, lot #, and % purity: fluvoxamine maleate; lot # 35572; 99.6% pure (amounts of impurities are presented in table 3, above); Certificate of Analysis, dated 10/26/00, page 929.

Methods

Doses: 0, 60, 120, 240 mg/kg.

Species/strain: male and female albino rats _____: CD@ (SD) IGS BR VAF/Plus®, _____; ~2 ½ months old at start of dosing.

Number/sex/group: 25/sex/group.

Housing: individually in stainless steel, wire-bottomed cages, except that each mating pair was housed in the male's cage during cohabitation; food and water *ad libitum*.

Route, formulation, volume, and infusion rate: oral gavage, once daily; as a slurry in McIlvaine's buffer (citric acid/sodium phosphate, pH4.5-5.0),

b(4)

b(4)

maintained on a magnetic stirrer, 8 ml/kg; doses were adjusted daily for changes in body weights.

Satellite groups used for toxicokinetics: none.

Study design: male rats were dosed for 28 day prior to cohabitation and continuing until the day before sacrifice (); females were dosed for 15 days prior to cohabitation and until gestational day 7 (sacrifice was on GD13). Estrous was evaluated by vaginal cytology for 14 days before cohabitation and until spermatozoa were observed in vaginal smear and/or copulatory plug *in situ* (for up to 14 days; if mating had not occurred, the female was paired for 7 days with another male from that dosing group that had already mated with another female).

Parameters and endpoints evaluated: (see below) gross necropsy of thoracic, abdominal, and pelvic viscera, weights on brain, pituitary, heart, liver, spleen, kidneys, testis (males), ovaries and gravid uterus (females); for males: epididymis, seminal vesicles (with fluid), and prostate; from left vas deferens or left cauda epididymis, sperm concentration and motility (by computer-assisted sperm analysis); for females: implantation sites, corpora lutea; for all rats: histopathology on liver, spleen, lungs, lymph nodes and kidneys.

Results

Mortality: The **moribund sacrifice of a HDM was considered drug-related**; 2 other deaths (a control male and LD female) were considered gavage accidents. The death of the HD male (on day 22, before it would have been mated) was attributed to drug; 77g weight loss between days 7 and 22, decreased food consumption, rales, chromorhinorrhea, urine stained abdominal fur, red perioral substance, and abdominal distention; with intestines distended with gas at necropsy. The death of the control male (on day 42) was considered accidental, evidenced by a broken palate, with chromodacryorrhea, chromorhinorrhea, and excess salivation (on day 42); this rat had mated and the female was pregnant. The death of the LD female (on GD 6) was considered accidental, evidenced by a small depression on the right kidney and ~7 ml of red fluid in the thoracic cavity at necropsy, with normal weight gain and food consumption prior to death; this female was pregnant.

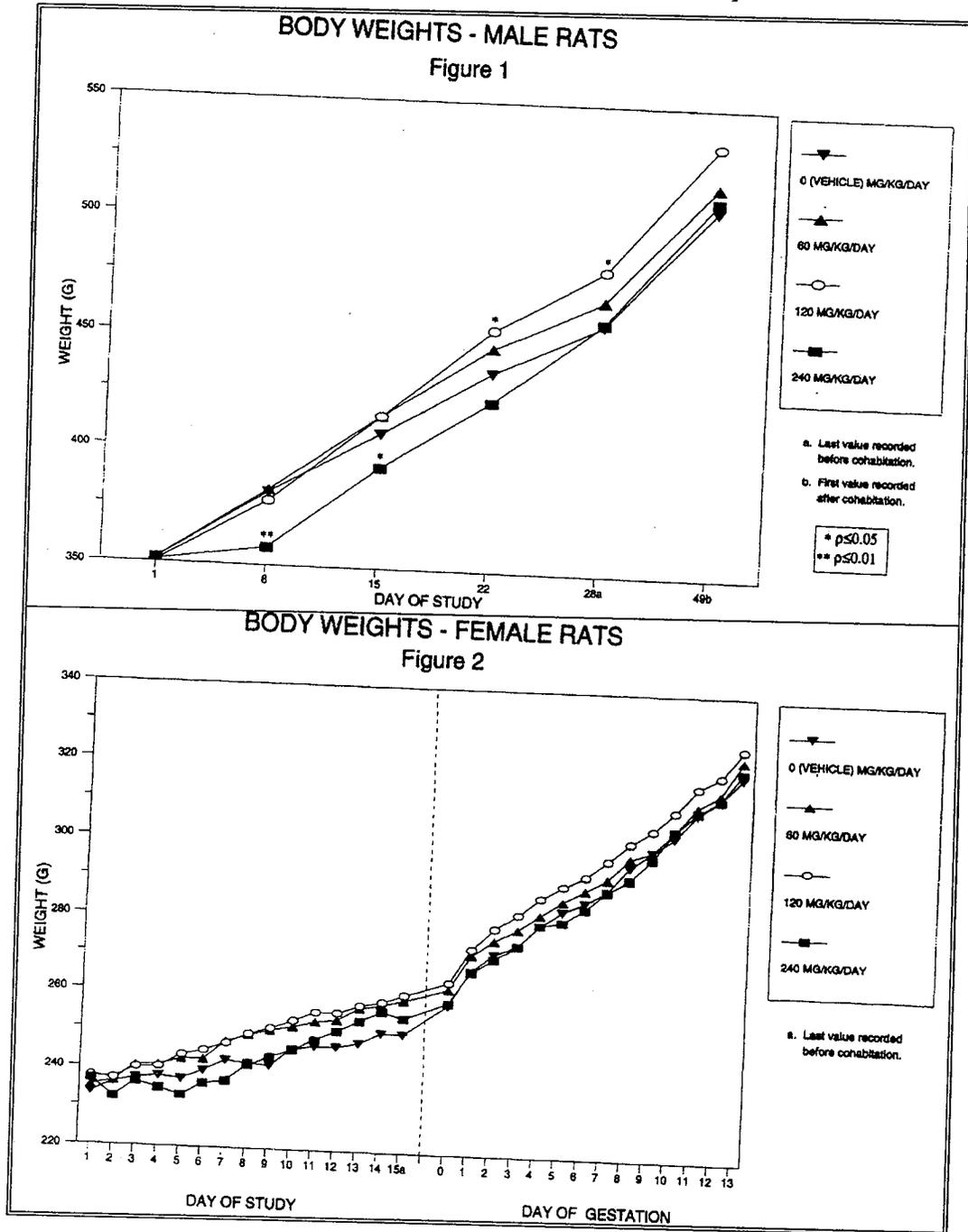
Clinical signs: Males: dose-related increased in number of males with chromorhinorrhea across doses; excess salivation and perioral substance at MD and HD; rales and urine-stained abdominal fur at HD.

Females: increased number of HD females with rales and perioral substance prior to cohabitation and during gestation; and excessive salivation during gestation.

Body weight: (daily): HD males gained less weight than controls during the first week of dosing (6.3 g, vs 29.5 g for controls), but gained at a rate similar to controls in subsequent weeks, and weighed the same as controls after 4 weeks of dosing, when pairing/mating occurred. MD males weighed slightly (4-5%) more than controls after 3 weeks and 4 weeks of dosing. (See table, below.)

Body weights for females were essentially unaffected by the 15 days of dosing prior to pairing or the 8 days of dosing during gestation (see figure, below).

Figure 1. Body weights of male and female rats treated with fluvoxamine maleate by oral gavage prior to mating (and during gestation for females). [Sponsor's graphs excerpted directly from pages 715 and 716 of this submission.]



Food consumption: (measured daily, except during cohabitation): HD males ate 23% less than controls during the first week of dosing when their body weight gain was low; during the following 3 weeks of dosing, their food consumption was similar to controls. LD and MD males ate slightly more than controls during weeks 2-4 of dosing; 6-8% for LD and 7-14% for MD.

Prior to gestation, HD females consumed 19% less food than controls during the first week of dosing. This decreased food consumption was no longer evident during week 2. During gestation, HD females consumed slightly less (8%) than controls during GD 0-8, but consumed considerably more (18%) than controls on GD 8-13; overall food consumption from GD 0-13 was similar for HD and controls (and other dosed groups).

Toxicokinetics: not done.

Necropsy: Males (after confirmation of pregnancy): At HD, **decreased weights of epididymis** (left ↓7%, statistically significant; right ↓5%, but non-significantly) and cauda epididymis (↓ left, ↓10%) compared with controls, but no effect on testes, seminal vesicles, prostate; increased liver weights at LD (↑10%), MD (↑17%), and HD (↑21%) and paired kidney weights at MD (↑12%) and HD (↑8%).

Females: (on gestational day 13): Increased liver weights at MD (↑9%) and HD (↑14%); increased lung weights (↑12%) and paired **ovary weights** (↑18%) at HD only.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

Males: **Sperm count was 28% lower** for HD males than for controls; sperm count was also lower (↓23%) at MD, but not statistically significantly. The "sperm density," i.e., sperm per gram of (left) caudal epididymis, was also lower (↓20%) at HD compared with controls, but not statistically significantly. No alterations in sperm motility were apparent.

Appears This Way
On Original

Table 3. Caudal epididymal sperm analysis for male rats. [Sponsor's summary table, excerpted directly from page 729 of this submission.]

TABLE B11 (PAGE 1): CAUDA EPIDIDYMAL SPERM MOTILITY, COUNT AND DENSITY - SUMMARY - MALE RATS																
DOSAGE GROUP		I			II			III			IV					
DOSAGE (MG/KG/DAY)		0 (VEHICLE)			60			120			240					
RATS TESTED		N			24a			25			25			24a		
NUMBER MOTILE	MEAN ₂ S.D.	316.6	±	92.6	335.1	±	90.1	325.3	±	84.0	282.6	±	68.6			
MOTILE PERCENT	MEAN ₂ S.D.	90.2	±	8.0	89.7	±	4.9	88.7	±	5.1	82.3	±	10.3			
STATIC COUNT (NONMOTILE)	MEAN ₂ S.D.	32.9	±	21.2	37.8	±	17.8	39.9	±	17.5	62.7	±	42.7			
TOTAL COUNT b	MEAN ₂ S.D.	349.5	±	93.8	372.9	±	96.1	365.2	±	86.8	345.2	±	78.3			
SPERM COUNT c	MEAN ₂ S.D.	148.2	±	67.7	148.7	±	71.4	113.5	±	41.2	107.2	±	55.9**			
DENSITY d	MEAN ₂ S.D.	1408.90	±	580.00	1376.20	±	614.80	1141.10	±	367.60	1122.10	±	509.60			

a. Excludes values for rats that were moribund sacrificed.
b. Sum of number motile and static count. Groups of five fields were evaluated until a sperm count of at least 200 was achieved or 20 fields were evaluated.
c. Sperm count used in the calculation of sperm density. Ten fields were evaluated.
d. The sperm density was calculated by dividing the sperm count by the volume in the image area (34.3 x 10⁻⁶ mL), multiplying by 2 (dilution factor) and multiplying by 10⁶ to obtain the sperm concentration. The calculated sperm concentration value (rounded to 1 decimal place) was multiplied by 50 (volume) and divided by the weight of the left cauda epididymis (see Table B17 for the weight of the left cauda epididymis) to obtain the sperm density. The calculated value will vary by approximately 0.8% from the Computer Automated Sperm Analysis because the digital image evaluated is slightly smaller (4 pixels) than the actual field causing a slight underestimate of the actual volume and an overestimate of the concentration.
** Significantly different from the vehicle control group value (p<0.01).

Females: Most females mated with the first paired-male, however, **the latency to mating was ~2-fold longer at MD (non-significantly) and HD**, compared with controls (see table, below). There was a suggestion of **decreased pregnancies at MD**, where only 88% (i.e., 21/24) of mated females were pregnant, **and HD**, where only 80% (i.e., 20/25) of mated females were pregnant, compared with 96% (i.e., 24/25) of mated controls. There were no statistically significant differences in numbers of corpora lutes, implantations, viable embryos or non-viable embryos. However, mean values for numbers of **implantations, viable embryos and non-viable embryos were 12, 10, and ~30% lower at HD** than in controls, consistent with a slight decrease in pre-implantation loss at HD (see table, below).

Appears This Way
On Original

Table 4. Mating and fertility variables for female rats during co-habitation. [Sponsor's table excerpted directly from page 814 of this submission.]

TABLE C10 (PAGE 2): MATING AND FERTILITY, ESTROUS CYCLING AND DAYS IN COHABITATION - SUMMARY - FEMALE RATS					
DOSAGE GROUP DOSAGE (MG/KG/DAY) ^a		I 0 (VEHICLE)	II 60	III 120	IV 240
MATING OBSERVATIONS					
RATS IN COHABITATION	N	25	25	25	25
DAYS IN COHABITATION	MEAN±S.D.	2.7 ± 4.0	2.4 ± 2.3	4.8 ± 6.1	5.0 ± 4.8**
RATS THAT MATED	N(%)	25(100.0)	25(100.0)	24(96.0)	25(100.0)
FERTILITY INDEX ^b	N/N (%)	24/ 25 (96.0)	25/ 25 (100.0)	21/ 24 (87.5)	20/ 25 (80.0)
RATS WITH CONFIRMED MATING DATES	N	25	25	24	25
MATED BY FIRST MALE ^c					
DAYS 1-7	N(%)	23(92.0)	24(96.0)	20(83.3)	22(88.0)
DAYS 8-14	N(%)	0(0.0)	1(4.0)	2(8.3)	1(4.0)
MATED BY SECOND MALE ^c					
DAYS 15-21	N(%)	2(8.0)	0(00.0)	2(8.3)	2(8.0)
RATS PREGNANT/RATS IN COHABITATION	N/N (%)	24/ 25 (96.0)	25/ 25 (100.0)	21/ 25 (84.0)	20/ 25 (80.0)

a. Dosage occurred on day 1 of study through day 7 of presumed gestation.
b. Number of pregnancies/number of rats that mated.
c. Restricted to rats with a confirmed mating date.
** Significantly different from the vehicle group value (p<0.01).

Table 5. Fertility variables for female rats. [Sponsor's table, excerpted directly from page 815 of this submission.]

TABLE C11 (PAGE 1): CAESAREAN-SECTIONING AND LITTER OBSERVATIONS - SUMMARY - FEMALE RATS					
DOSAGE GROUP DOSAGE (MG/KG/DAY) ^a		I 0 (VEHICLE)	II 60	III 120	IV 240
RATS TESTED	N	25	25	25	25
PREGNANT	N(%)	24(96.0)	25(100.0)	21(84.0)	20(80.0)
FOUND DEAD	N(%)	0(0.0)	1(4.0)	0(0.0)	0(0.0)
RATS PREGNANT AND CAESAREAN-SECTIONED ON DAY 13 OF GESTATION	N	24	24	21	20
CORPORA LUTEA	MEAN±S.D.	17.4 ± 2.3	17.2 ± 3.6	17.8 ± 2.0	16.8 ± 3.7
IMPLANTATIONS	MEAN±S.D.	15.2 ± 3.3	15.2 ± 3.6	15.7 ± 3.3	13.4 ± 4.5
VIABLE EMBRYOS	N	338	338	307	254
MEAN±S.D.		14.1 ± 3.2	14.1 ± 4.1	14.6 ± 3.4	12.7 ± 4.2
NONVIABLE EMBRYOS	N	26	27	22	15
MEAN±S.D.		1.1 ± 1.3	1.1 ± 1.8	1.0 ± 1.0	0.8 ± 0.8
DAMS WITH ANY NONVIABLE EMBRYOS	N(%)	13(54.2)	12(50.0)	15(71.4)	12(60.0)
DAMS WITH ALL NONVIABLE EMBRYOS	N(%)	0(0.0)	1(4.2)	0(0.0)	0(0.0)
DAMS WITH VIABLE EMBRYOS	N(%)	24(100.0)	23(95.8)	21(100.0)	20(100.0)
PLACENTAE APPEARED NORMAL	N(%)	24(100.0)	23(100.0)	21(100.0)	20(100.0)
‡ NONVIABLE EMBRYOS/LITTER	MEAN±S.D.	6.8 ± 8.1	7.3 ± 12.3	7.0 ± 6.3	5.0 ± 5.6

a. Dosage occurred on day 1 of study through day 7 of gestation.

1.4 Segment II study in rats: Embryo-fetal development.

Study title: Oral (gavage) developmental toxicity study of fluvoxamine maleate in rats.

Key study findings:

- At doses of 0, 60, 120, and 240 mg/kg;
- Maternal toxicity at HD: 1 death; and decreased terminal weights (with or without gravid uterine weights);
- Developmental NOAEL = 60 mg/kg: increased resorptions and increased incidence of eye abnormality (folded retina(s)) at ≥ 120 mg/kg; decreased fetal weights, decreased live litter size, and decreased number of ossified metatarsals at 240 mg/kg.

Study no.: [REDACTED] study no. 4019022; Solvay's report no. TX.114.07.05P CRO.

Volume #, and page #: volume 4, pages 1210-1551.

Conducting laboratory and location: [REDACTED]

Date of study initiation: dosing (GDs 7-17) on 3/2/01-4/2/01.

GLP compliance: yes, see page 1548.

QA reports: yes, see pages 1550-1551.

Drug, lot #, and % purity: fluvoxamine maleate; lot # 35572; 99.6% pure (amounts of impurities are presented in table 3, above); Certificate of Analysis, dated 10/26/00, page 1510.

Methods

Doses: 0, 60, 120, and 240 mg/kg.

Species/strain: female albino rats [REDACTED]: CD®(SD)IGS BR BR BAF/Plus®, [REDACTED]

[REDACTED]; and male breeder rats; randomly assigned to dosing groups, based upon body weights on GD0;

Number/sex/group: 25 presumed-pregnant female rats/dose-group.

Housing: individually in stainless steel, wire-bottomed cages, except that each mating pair was housed in the male's cage during cohabitation; food and water *ad libitum*.

Route, formulation, volume, and infusion rate: oral gavage, once daily for days 7-17 of presumed gestation (GD0, spermatozoa in vaginal smear and /or copulatory plug *in situ*); as a slurry in McIlvaine's buffer (citric acid/sodium phosphate, pH4.5-5.0), maintained on a magnetic stirrer, 8 ml/kg; doses were adjusted daily for changes in body weights.

Satellite groups used for toxicokinetics: not performed.

Study design: 144 virgin females were paired with 144 breed males for up to 5 days; GD0 was determined by spermatozoa in vaginal smear and /or copulatory plug *in situ*); presumed-pregnant females were randomly assigned to dosing groups, based upon body weights on GD0; all rats were sacrificed by CO2

b(4)

b(4)

asphyxiation on GD21; gross pathology on thoracic, abdominal, and pelvic viscera, organs weights for gravid uterus, brain, pituitary, heart, liver, spleen, kidneys, and ovaries, histopathology on liver, spleen, lungs, lymph nodes, and kidneys, and number of corpora lutea in ovaries of dams; all fetuses weighed and examined for sex and gross external alterations; ~half of each litter were fixed in Bouin's solution, stored in alcohol, and examined for soft tissue alterations; the other half of each litter were initially fixed in alcohol, retained in glycerin with thymol, and examined for skeletal alterations, after staining with alizarin red S. Parameters and endpoints evaluated: standard (see tables, below).

Results

Mortality (dams): 1 HD female (#19490) was found dead on day 19 of gestation (GD19); with litter comprised of 7 late and 6 early resorptions; red vaginal substance noted on GD15 and GD17; excess salivation noted on GD15. The report attributed this death to drug, since it occurred at the HD, but no clear cause of death was identified.

Clinical signs (dams): at HD, increased number of dams with excessive salivation, red substance around vagina, rales, and urine-stained abdominal fur.

Body weight (dams): Effects were limited to the HD group. Terminal body weights (GD21) were slightly decreased at HD ($\downarrow 11\%$, which is ~ 48 g, vs controls); terminal body weights corrected for gravid uterine weights were similarly decreased at HD ($\downarrow 11\%$); gravid uterine weights were similarly decreased at HD ($\downarrow 12\%$ vs controls, averaged 112g for controls and 99g for HD); body weights of HD dams were decreased compared with controls from GD8 through GD19. Heart weights were also decreased at HD (absolute $\downarrow 11\%$; relative to brain $\downarrow 12\%$).

Food consumption (dams): average food consumption was decreased $\sim 30\%$ throughout dosing (GD7-18) at HD; decreased 15% for GD7-10, then 7-9% throughout the rest of dosing at MD; decreased $\sim 9\%$ for GD7-10 only at LD.

Toxicokinetics: not performed.

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

Fluvoxamine maleate administered during gestational days 7-17 (i.e., during organogenesis, but after implantation) did not alter pre-implantation losses (or numbers of corpora lutea or implantations), but did increase early and late resorptions (see table, below). Early, late, and total resorptions were significantly increased at both MD (not statistically significantly) and HD; mean total **resorptions were increased ~ 3 -fold in MD litters and ~ 7 -fold in HD litters**, compared with controls. This effect was also seen in the number of dams that had any resorptions: 28% of controls compared with 44% of MD dams and 83% of HD dams.

Table 6. Maternal variables for Segment II study of 0, 60, 120, and 240 mg/kg oral (gavage) doses of fluvoxamine maleate in rats.

PARAMETER	DOSE, mg/kg/d (gestational D7-17)			
	0	60	120	250
Total pregnancy rate	25/25	25/25	23/25	24/25
Mortalities	0	0	0	1
Pregnant Females at termination	25	25	23	23
Mean implantation sites	16.1	17.0	16.6	17.0
Mean corpora lutea	19.2	19.8	20.2	20.2
Pre-implantation loss, %, per dam	~16	~14	~18	~16
Mean live fetuses	15.6	16.8	15.3	13.2
Mean dead fetuses	0.0	0.0	0.0	0.1
Mean early resorptions	0.4	0.2	1.2	2.0*
Mean late resorptions	0.0	0.0	0.2	1.7*
Mean total resorptions	0.5	0.2	1.3	3.7*
% dead or resorbed conceptuses/litter	2.8%	1.1%	6.2%	22.4%*
Dams with any resorptions	7 (28%)	4 (16%)	10 (44%)	19 (83%)*

Offspring (malformations, variations, etc.):

Fluvoxamine maleate appeared to **decrease litter size at the HD**; the number of live fetuses per litter was 15% lower (not statistically significant) at the HD. Additionally, **mean fetus weights were significantly decreased ~15% at the HD** (but not at lower doses) for both male and female fetuses (see table, below).

According to the study report, there were no soft tissue malformations (see "folded retinas" discussed under alterations, below). Skeletal malformations were limited to 1 control fetus with gross external malformations (craniorachischisis, depressed eye bulge, and protruding tongue) and skull and vertebral malformations and 1 fetus from a LD litter with gross external malformations (exencephaly, depressed eye bulges, protruding tongue, narrow snout, and fleshy protrusion above oral opening) and skull malformations.

There were apparent increases in the incidence of "alterations" at all doses, but particularly at the HD, where there was a significant increase in fetuses with any alterations (15%, compared with 1.3% in controls), see table, below. This was largely due to **the increased incidence of folded retinas** that were observed in 3% of MD fetuses (18% of MD litters) and 19% of HD fetuses (65% of HD litters), but none of the control or LD fetuses. [A search of the Historical Control Data Base: A Joint Project of MARTA and MTA (www.hcd.org) in this rat strain (CD(SD)IGS BR) on gestational day 21 from 1997 to the present found only 14 affected fetuses out of 7067 evaluated (from 1013 litters evaluated from 43 studies.) Additional visceral findings included slightly increased incidences of renal pelvis dilation, consistent with retarded development, and umbilical artery descending to the left of the bladder, a variation.

b(4)

Skeletal findings were limited to slightly **decreased mean number of fetuses with ossified metatarsals**, an indication of retarded development, and possibly a slightly increased incidence of cervical rib at the 7th cervical vertebra at the HD, a variation (see table, below).

Table 7. Embryo/fetal variables for Segment II study of 0, 60, 120, and 240 mg/kg oral (gavage) doses of fluvoxamine maleate in rats.

PARAMETER	DOSE, mg/kg/d (gestational D7-17)			
	0	60	120	240
Mean live fetuses/litter	15.6	16.8	15.3	13.2
Males per litter	7.5	8.2	7.6	6.7
Mean % males	47.9%	48.7%	45.6%	51.0%
Mean fetus weights, g, males	5.25	5.27	5.27	4.50*
Mean fetus weights, g, females	4.98	5.05	4.97	4.24*
Total litters examined	25	25	22	23
Total fetuses examined for external alterations	391	421	352	303
Total fetuses examined for soft tissue alterations	189	206	167	145
Total fetuses examined for skeletal alterations	202	215	185	158
Litters with fetuses with any alterations observed	4	10	9	19*
Fetuses with any alterations observed (%)	5 (1.3%)	19 (4.5%)	14 (4.0%)	46* (15%)
% fetuses with any alteration/litter	1.2%	4.5%	4.4%	16%*
Soft tissue alterations:				
Eye: folded retina, litter incidence (%)	0 (0.0%)	0 (0.0%)	4 (18%)	15 (65%)*
fetal incidence (%)	0 (0.0%)	0 (0.0%)	5 (3.0%)	27 (19%)*
Kidney: dilation of pelvis (slight-moderate), litters (%)	1 (4.0%)	3 (12%)	3 (14%)	5 (22%)
fetuses (%)	2 (1.0%)	4 (1.9%)	3 (1.8)	7 (4.8%)
Umbilical artery descends to left of bladder, litters (%)	1 (4%)	2 (8%)	4 (18%)	4 (17%)
fetuses (%)	1 (0.5%)	2 (1%)	5 (3%)	4 (3%)
Skeletal alterations:				
Hind limb, metatarsals ossified, mean per fetus / litter	4.71	4.70	4.74	4.38*
Cervical rib at 7 th cervical vertebra, litters (%)	0 (0%)	6 (24%)	2 (9%)	4 (17%)
fetuses (%)	0 (0%)	7 (3%)	2 (1%)	5 (3%)*

1.5 Summary and Conclusions for Reproductive toxicity studies:

The Sponsor has submitted new Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproductive toxicology studies for review in support of the current submission.

In the Segment I (fertility and early embryonic development) study, doses of 60, 120, and 240 mg/kg were administered orally to both male and female rats: to male rats for 28 day prior to and during mating; and to female rats for 15 days prior to and during mating and through gestational day 7 (GD 7) with sacrifice on GD 13. The NOAEL for fertility appeared to be 60 mg/kg, based upon decreased sperm count and epididymis weight in

males, increased days in cohabitation until mating, and decreased pregnancies at doses ≥ 120 mg/kg. At 240 mg/kg, the number of implantations and viable and non-viable embryos were decreased (in females).

In the Segment II (embryo-fetal development) study, doses of 60, 120, and 240 mg/kg were administered orally to pregnant female rats during the period of organogenesis (i.e., GD 7-17), with sacrifice on GD 21. The NOAEL for developmental effects appeared to be 60 mg/kg, based upon increased resorptions and increased incidence of an eye abnormality (folded retina(s)) at ≥ 120 mg/kg; and decreased fetal weights, decreased live litter size, and decreased number of ossified metatarsals at 240 mg/kg.

The increased occurrence of the rarely-reported eye abnormality, folded retinas, at 120 and 240 mg/kg is worrisome, given the seriousness of eye defects and the finding of retinal abnormalities in adult rats administered another SSRI (citalopram) in a 2-year carcinogenicity study (see Celexa labeling, 2003 PDR). The Sponsor (i.e., the study report) considers this finding a variation and suggests that "This observation [of folded retina(s)] is generally considered a processing artifact, however, the increase in this observation in the 240 mg/kg dosage group may be associated with the small size of the fetuses in this group" (quoted from the results section 3.7.2.1 Eyes/Variations/Fetal Soft Tissue Alterations, on page 1239 of the study report; also repeated in the Conclusion Section 4.0 and Summary and Conclusions Sections 1.3 and 1.4). However, this possible explanation cannot serve to dismiss our concern about the finding.

Pilot and dose-range finding mating and fertility studies determined that both male and female rats died at doses ≥ 320 mg/kg, so limiting dosing to a maximum dose of 240 mg/kg in the Segment I (fertility and early embryonic development) and II reproductive toxicology studies appears justified. Additionally, decreased body weights and a single death in males in the Segment I (fertility and early embryonic development) study and decreased body weights (corrected for uterine weights) and a single death in females in the Segment II (embryo-fetal development) study are evidence that the dose of 240 mg/kg at least an MTD in the current studies. This dose of 240 mg/kg is 3-times the high dose of 80 mg/kg that was determined to be inadequate in the original studies reviewed for NDA 20-243. Toxicokinetic analysis, in dose-range finding studies, determined systemic exposures of 23 and 32 $\mu\text{g}\cdot\text{hr}/\text{ml}$ in male and female rats, respectively, after ~4-5 weeks of dosing at 240 mg/kg.

The NOAEL of 60 mg/kg for both fertility and developmental toxicity gives a 2-fold safety margin for the maximum recommended daily human dose of 300 mg in adults.

Appears This Way
On Original

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

2 IMPURITY AND DEGRADANT ISSUES:

2.1 History/Background:

In a letter dated 9/5/02 in reference to NDA 21-519, the Agency requested additional information regarding Biopharmaceutics, Chemistry, Manufacturing, and Controls (CMC), and Pharmacology/Toxicology. Specifically relevant to qualification of degradants in the drug product, CMC Question #3 noted that several of the proposed specifications for Luvox drug product exceeded the 0.2% threshold for qualification of degradation products as described in the "Guidance for Industry-Q3B Impurities in New Drug Products;" and asked that the Sponsor provide a rational and justification for the selection of those degradation product limits. [This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27454).]

The Sponsor addressed the issues raised by the Agency's 9/5/02 letter in a submission to NDA 21-519 (letter-dated 5/7/03). Specifically, the Sponsor stated:

"The specification levels proposed in NDA 21-519 for the LUVOX® drug product degradants are based on the specification levels previously approved in NDA 20-243 except for a correction due to a calculation error. This calculation error was discovered during a FDA site audit and submitted as a Changes Being Effected supplement to NDA 20-243 on 22 October 1998. On 30 April 1999 Solvay Pharmaceuticals Inc. was informed that no action concerning this supplement would be taken by the FDA until we were removed from AIP. For your convenience, the entire supplement previously submitted to NDA 20-243 on 22 October 1998, is provided in Attachment 8."

In the response above, the Sponsor refers the Agency to Attachment 8 (volume 7, pages 2019-2162) [This supplement was previously submitted to NDA 20-243 on 10/22/98]. Specifically, the "toxicity information in support of the revised related compound limits in tablets" is presented in Attachment III (pages 2134-2136). This information was not reviewed at the time of submission, because of the AIP audit, however, it will be reviewed here in support of the currently proposed specifications.

During the review cycle of the current NDA (21-519) submission additional impurity issues arose. The reviewing Chemist (Lorenzo Rocca, Ph.D.) brought to my attention that the specifications for several impurities in drug substance were also set above qualification threshold. On 10/30/03, a Deficiency Letter to the Sponsor's DMF ~~_____~~ specifically addressed this issue for the drug substance (among other Chemistry issues), informing the Sponsor that:

"The FDA recommends that the DMF Holder [i.e., the Sponsor, Solvay Pharmaceuticals] lower the release and retest specifications for the identified impurities in fluvoxamine maleate drug substance so as to be consistent with the

b(4)

ICH Q3A(R) *Impurities in New Drug Substances* (i.e., NMT 0.15%) Guidance. Alternatively, please provide the FDA with data or references to the data that qualifies the fluvoxamine maleate drug substance impurities as listed in the current release and retest specifications.”

[As far as I am aware, the Sponsor had not responded to this letter as of 1/23/04.]

2.2 Current status:

For Luvox, with a maximum recommended human daily dose of 300 mg, the threshold for qualification of impurities in drug substance is 0.15% (ICH Q3A (revision 1) Guidance, 2003), which is higher than the earlier recommended 0.1% threshold (ICH Q3A Guidance, 1996), and the threshold for qualification of degradants in drug product is 0.2% (ICH Q3B Guidance, 1996). The specifications for impurities in drug substance and drug product, as currently proposed under NDA 21-519 and as originally approved under NDA 20-243, are presented in the table, below.

Table 8. Release specifications for impurities currently proposed (under NDA 21-519) compared with those that were originally approved (under NDA 20-243) for drug substance and drug product. Only drug substance impurities with specifications above the 0.15% qualification threshold and drug product impurities/degradants above the 0.2% qualification threshold are presented.

b(4)

Values originally approved for the drug substance are from DMF — Review #2, by Lorenzo Rocca, Ph.D., dated 10/30/03; other values are from Dr. Rocca's Chemistry Review of NDA 21-519, dated 1/29/03; after consultation with Dr. Rocca.

In the drug substance, the proposed specifications for — impurities have been set above the qualification threshold of 0.15%; —

— The currently proposed specifications for each of these impurities, though above the qualification threshold, is less than or equal to that approved in 1994 under NDA 20-243. Additionally, the specification for —

b(4)

_____ has been lowered from the originally approved specification of _____ to 0.15%, a specification that does require qualification.

b(4)

In the drug product, the proposed specifications for _____ of the impurities in the drug substance have been set above the qualification threshold of _____. It should be noted that the specification proposed for the _____ in the drug product is the same as that approved for this product under NDA 20-243 and that the specifications proposed for the other impurities/degradants, the _____ are slightly higher than those approved under NDA 20-243. It is also of interest that the specifications for these _____ impurities/degradants are higher for the drug product than for the drug substance, suggesting that they are degradation products as well as being process impurities in the drug substance.

b(4)

In conclusion, a total of _____ impurities/degradants require qualification: _____ impurities/degradants _____ are currently specified at amounts requiring qualification in drug product (or drug product and drug substance) and _____ more exceed the qualification threshold only in drug substance _____

b(4)

2.2.1 The Sponsor's response to the Agency's request for justification of specifications above the qualification threshold for degradants in drug product.

On 9/5/02, a letter was sent to the Sponsor requesting (among other things) that the Sponsor provide a rationale and justification for their selection of specifications for degradants in drug product in NDA 21-519 that exceeded the qualification threshold (i.e., >0.2%). The Sponsor addressed the Agency's concerns in their 5/7/03 submission by referencing (and resubmitting to the current NDA 21-519) an earlier submission (letter-dated 10/22/98) to NDA 20-243. Attachment III (pages 2132-2139) of that submission contained "toxicity information in support of the revised related compound limits in tablets" and is summarized below.

Regarding the main impurity, the addition product, the Sponsor cited a 13-week oral toxicity study in rats where fluvoxamine maleate was compared with fluvoxamine maleate containing _____ (referencing report no. 3110-65/7, by _____; Duphar document no. 56645/14/83). The Sponsor claimed that no additional toxicity was observed that could be attributed to the _____. In a review (stamp-dated 6/28/85) for a submission (dated 11/26/84) to NDA _____ sponsored by Kali-Duphar Laboratories, Inc., and used in support of NDA 20-243), Barry Rosloff, Ph.D., reviewed a 13-week oral toxicity study in rats, using a fluvoxamine _____ which he noted was said to be an "impurity/degradation product" which increases during storage,

b(4)

but that its structure was not provided. Dr. Rosloff concluded that "there were no clearly drug-related effects on the usual toxicologic parameters, including lab tests and histopathology," but only a single, low dose of 9 mg/kg fluvoxamine maleate was tested with or without _____ added (a vehicle control was also included). It is this Reviewer's opinion that the low dose of fluvoxamine, while not adequate to identify toxicity due to fluvoxamine, should be useful for identifying additional toxicity due to the _____. Furthermore, the _____ dose of the _____ would be equivalent to a _____ for a 60-kg human, on a mg/m² basis. This is more than 3-fold the currently-proposed _____ specification for this impurity in drug product (i.e. _____ of impurity at the maximum recommended human dose [MRHD] of 300 mg in a 60-kg human, on a mg/m² basis) and ~10-fold the currently-proposed _____ specification for drug substance (i.e., _____ of impurity at the MRHD of 300 mg in a 60-kg human, on a mg/m² basis).

b(4)

Regarding the other impurities, the Sponsor stated that no other toxicity data are available, because most of the impurities were detected after the non-clinical studies had been performed. However, the Sponsor suggests that it is likely that these impurities were also present in the drug substance used in the toxicity studies, at amounts even higher than the current product specifications. In support of this contention, the Sponsor has presented a table showing the specifications for several impurities/degradants in drug substance during years 1983-1993, see below.

Table 9. Historical specifications for "related substances" in fluvoxamine maleate drug substance. [Sponsor's table, excerpted directly from electronic submission to NDA 21-519 dated 5/7/03, Attachment III, volume 7, page 2135.]

- not specified; * not changed

b(4)

It should be noted that **actual amounts of the impurities were not provided**, only the specifications.

The Sponsor also cited the considerable human exposure to older formulations of fluvoxamine maleate in more than 40 countries between 1983 and 1997, where the specifications for _____ were considerably higher (i.e., _____ respectively) than those currently proposed (i.e., _____ respectively). Additionally noted were the approvals in late 1993 in Canada, Sweden, the United

b(4)

for impurities in drug product. Furthermore, it should be noted that: _____ and the _____ higher specifications for drug product than for drug substance. b(4)

According to the current ICH Guidances (Q3A and Q3B), if specifications for these impurities/degradants cannot be lowered adequately, then studies required for qualification, based upon the patient population and duration of use, would include:

- A general toxicology study in on species, of 14-90 days duration;
- *In vitro* genotoxicity studies (for point mutations and for chromosomal aberrations);
- Other specific toxicity endpoints, as appropriate (see below).
 - a Segment II (embryo-fetal development) reproduction study in one species (because this indication (i.e., OCD) is chronic and the patient population includes women of child-bearing potential);
 - a juvenile animal study in one species (because the Sponsor is proposing use in a pediatric population).

The 13-week general toxicology study in rats (using drug substance with 10% addition product) cited by the Sponsor would fulfill the general toxicology qualification requirement for the addition product.

Furthermore, the qualification requirement for a Segment II (embryo-fetal development) reproductive toxicology study has been met for some of the impurities/degradants (but _____ by the Segment II reproductive toxicology study submitted to the current NDA (21-519) in fulfillment of a Phase IV commitment for NDA 20-243. b(4)

However, none of the impurities/degradants appear to have been assessed for genotoxicity or for toxicity in juvenile animals.

Appears This Way
On Original

3 OVERALL CONCLUSIONS AND RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, this NDA is Approvable.

The Phase IV commitment for NDA 20-243, to conduct repeat Segment I (mating and fertility) and Segment II (embryo/fetal development) reproductive toxicology studies in rats, using adequate doses, has been fulfilled by the studies provided to NDA 21-519. Labeling will need to be changed to incorporate the results of these studies, including decreased fertility, litter size, and fetal weight and increased fetal abnormalities (specifically, folded retinas) (see revised labeling in Section 1.6 of this review, above).

Specifications set for several impurities are above the threshold for qualification in drug substance (i.e., above 0.15%) and/or drug product (i.e., above 0.2%). The specification set for _____ of the process impurities _____

_____ is only slightly above the qualification threshold (i.e., _____ vs 0.15%), which would result in a daily dose _____ instead of _____ (at the qualification threshold). Considering these low doses, it would seem reasonable to limit the need for qualification to an assessment of genotoxic potential (i.e., *in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]).

b(4)

The specifications set for the _____ impurities in the drug product _____ substantially exceed the qualification threshold _____ . If possible, the Sponsor should lower the specifications for these impurities to below the qualification threshold. If not, these impurities need to be qualified in the following studies, taking into consideration the intended indication and patient population:

b(4)

- a general toxicology study in one species, of 14-90 days duration; justification should be provided for the species selected;
- *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]);
- an embryo/fetal development study in one species; justification should be provided for the species selected; and
- a juvenile animal study; justification should be provided for the species selected.

The Sponsor provided "historical specifications" for "related substances" present in drug substance used or manufactured early in development (1983-1993). However, these data were not informative since neither actual amounts of the impurities nor batch numbers were provided. The Sponsor referred to a 13-week study in rats using drug substance that contained _____ this has been previously reviewed and will fulfill the general toxicology study requirement for this impurity. The Sponsor also provided a brief summary of specifications for _____ impurities _____ in clinical formulations marketed (since late 1993) in several foreign countries. To the extent that the Sponsor can provide documentation that the _____ have

b(4)

been qualified by this clinical use, no further testing of general toxicity would be needed. The embryo/fetal toxicity of the _____ was adequately assessed in the (Segment II) study of embryo-fetal development submitted to this NDA.

b(4)

Complete qualification of impurities, except for the juvenile study, will be needed prior to approval.

To support the use of Luvox in children, juvenile studies in 2 animal species (rat and dog) need to be conducted; this may be done after approval. The impurities should be qualified in 1 of these studies.

4 SIGNATURES

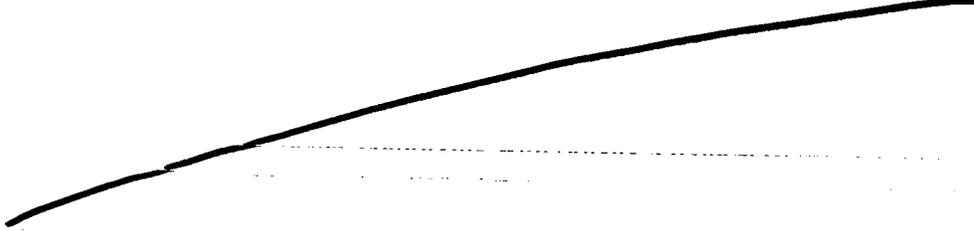
Linda H. Fossom, Pharmacologist *{see appended electronic signature page}*
Lois Freed, Supervisor *{see appended electronic signature page}*

5 APPENDIX:

In the preparation of the current review of NDA 21-519, the following reviews were consulted:

- Pharmacology/Toxicology Review of NDA 20-243 (sponsored by Solvay, for OCD), by Barry Rosloff, Ph.D. In his original review of NDA 20-243 (dated 3/10/92), Dr. Rosloff noted that commercial NDA _____ (sponsored by Kali-Duphar Laboratories, Inc.) for the use of fluvoxamine (maleate) as an _____ had been previously reviewed by him and considered approvable; he cited his previous reviews of that application (dated 11/30/84, 5/29/85, and 9/3/86), as well as a statistical review (7/18/85). He stated that "No new animal toxicity or ADME/PK studies were submitted with the present application."

b(4)

- 
- Chemistry Review of DMF _____ (describing manufacture of drug substance; held by Solvay), by Lorenzo Rocca, Ph.D. (dated 10/30/03).
 - Chemistry Review of NDA 21-519, by Lorenzo Rocca, Ph.D. (dated 1/30/04)

According to the Orange Book, there are several generic versions of fluvoxamine maleate are on the market in the US, all approved after Luvox under NDA 20-243, but during the AIP audit (see list, below). [There is no reference drug listed in the Orange Book for fluvoxamine maleate, however, it seems likely that the specifications originally approved for drug substance and drug product under NDA 20-243. in 1994 are the specifications that must be met by the generic formulations.]

1. ANDA 75-897; Barr; approved 1/25/01;
2. ANDA 75-888; Eon; approved 11/29/00;
3. ANDA 75-887; Geneva Pharms; approved 1/5/01;
4. ANDA 75-950; Genpharm; approved 10/15/01;
5. ANDA 75-898; Ivax Pharms; approved 3/12/01;
6. ANDA 76-125; Mutual Pharm; approved 4/29/02;
7. ANDA 75-889; Mylan; approved 11/29/00;
8. ANDA 75-901; Purepac Pharm; approved 12/28/00;
9. ANDA 75-899; Synthron Pharms; approved 1/17/01;
10. ANDA 75-893; Teva; approved 9/10/02;
11. ANDA 75-902; Torpharm; approved 5/7/01;
12. ANDA 75-894; Watson Labs; approved 4/18/01.

There are [redacted] other commercial NDAs for fluxoxamine maleate [redacted]
[redacted] and/or have been withdrawn:

- [redacted] **b(4)**
- [redacted]
- NDA 20-243, for use in OCD was Approved on 12/5/94; put on AIP from 9/24/94 to 4/9/03; and withdrawn on 9/3/03;
- [redacted] **b(4)**
- [redacted] **b(4)**

Appears This Way
On Original

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Fossom
2/9/04 07:28:03 AM
PHARMACOLOGIST

Lois Freed
2/9/04 08:08:30 AM
PHARMACOLOGIST
Please see my memo dated 2/9/04